SYNTHESIS AND UTILITY OF SOME *N*-SUBSTITUTED BENZOTRIAZOLES

By

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Most importantly, I thank my wife for everything that makes life pleasant.

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Abstract of Dissertation Presented to the Graduate School
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SYNTHESIS AND UTILITY OF SOME
BENZOTRIAZOLE-CONTAINING INTERMEDIATES

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Major Department: Chemistry

Making use of some of the versatile properties of the synthetic auxiliary benzotriazole, the synthesis and utility of several types of benzotriazole-containing intermediates has been explored.

The Reformatsky reaction of bromofluoroacetates with *N*-(*alpha*-aminoalkyl)benzotriazoles was developed, and its utility in the synthesis of mono- and di-fluorinated *beta*-amino esters demonstrated. In addition to supplementing other methods for synthesizing such compounds, this approach has led to the first synthesis of *alpha*-fluorinated bis(*beta*-amino esters).

An improved, high-yielding method for the synthesis of 1,4-, 1,2,4-, 1,3,4- and 4-substituted tetrahydroquinolines from *N*-(*alpha*-aminoalkyl)benzotriazoles and olefins was developed. Advantages of this method include the ability to use unactivated 1-alkenes and 1,2-disubstituted alkenes and to prepare *N*-unsubstituted and 2-substituted tetrahydroquinolines.

The scope and limitations of selected methods of synthesizing *alpha*-benzotriazolylenamines was explored, and the potential utility of said compounds as stable analogs to *alpha*-chloroenamines was demonstrated. A variety of *alpha*-(benzotriazol-1-yl)enamines were easily prepared as separated E and Z isomers in good overall yields from the action of benzotriazole, $POCl_3$ and NEt_3 on amides. Additionally, *N*-[(*E*)-1-(2*H*-1,2,3-benzotriazol-2-yl)-1-butenyl]-*N*-methylaniline was synthesized along with *N*-[(*Z*)-1-(1*H*-1,2,3-benzotriazol-1-yl)-1-butenyl]-*N*-methylaniline in moderate yield by reaction of *N*-(*trans*-buten-1-yl)-*N*-methylaniline with 1-chloro-1*H*-1,2,3-benzotriazole and *t*-BuOK. The utility of these stable com-pounds was demonstrated by the nucleophilic substitution of the benzotriazolyl moiety from *N*-[1-(2*H*-1,2,3-benzotriazol-2-yl)-2-methyl-1-propenyl]-*N*-methylaniline by phenylethynylzinc chloride to form *N*-methyl-*N*-[2-methyl-1-(2-phenylethynyl)-1-propenyl]aniline.

The synthesis of (*E*)-1-benzotriazolyl-3-(phenylsulfonyl)-1-propene and its reactivity towards electrophiles was investigated. The use of 2.1 equivalents of LDA and electrophile gave high yields of *alpha*, *alpha*-dialkylated products. The easy generation of the first carbanion and the carbanion of the monoalkylated compound, and also the regioselectivity in the alkylation of (*E*)-1-benzotriazolyl-3-(phenylsulfonyl)-1-propene, can be attributed to the greater capability of a sulfonyl group to stabilize an adjacent carbanion as compared to that of a benzotriazolyl group. The low reactivity of these carbanions toward electrophiles other than alkyl halides will limit the application of this method.

Thus, benzotriazole methodology has been further explored, and this work thereby resulted in a greater understanding of the benzotriazolyl group, better methods for the

synthesis of certain types of compounds and the synthesis of previously unknown entities.

CHAPTER 1
CHEMISTRY OF *N*-SUBSTITUTED BENZOTRIAZOLES

As recently reviewed [98CRV409], benzotriazole (**1.1**, BtH, Figure 1.1) is an inexpensive, stable and highly useful synthetic auxiliary, *i.e.*, it is (1) easily introduced at the beginning of a synthetic sequence, (2) stable during a variety of synthetic operations, (3) able to activate other parts of the molecule, and (4) easily removed at the end of the synthetic sequence. Research on the chemistry of *N*-substituted benzotriazoles has been a major interest of Katritzky and co-workers for 15 years, during which time substantial progress has been made in discovering some of the properties and synthetic utilities of these molecules.

1.1, Benzotriazole

1.2, Bt^1-R

1.3, Bt^2-R

Figure 1.1. Benzotriazole and Its *N*-Substituted Derivatives

N-Substituted benzotriazoles (Bt-R) can exist as either the benzotriazol-1-yl (**1.2**, Bt^1) or benzotriazol-2-yl (**1.3**, Bt^2) isomer. These two isomers are of the same order of stability and show similar reactivity. Depending on the functionalities adjacent to the Bt group, these isomers are known to interconvert in solution [87JCS(P1)2673].

Benzotriazole exhibits several useful properties. As well as activating an *alpha*-CH toward proton loss, Bt exhibits both electron-donor and electron-acceptor properties (Figure 1.2). The Bt group has been compared to a halogen substituent; however, Bt-containing compounds are much less reactive and more stable than their halogen-containing analogs. Additionally, when Bt-containing compounds have an *alpha*-heteroatom, the electronic properties of Bt facilitate ionization by cleavage of either the Bt-C bond (common for mono- or di-substituted amino, alkoxy, or thioalkoxy groups) or heteroatom-C bond (common for halogen or hydroxy groups). These properties will be further discussed as they pertain to the synthesis, reactions and removal of Bt from *N*-substituted benzotriazoles.

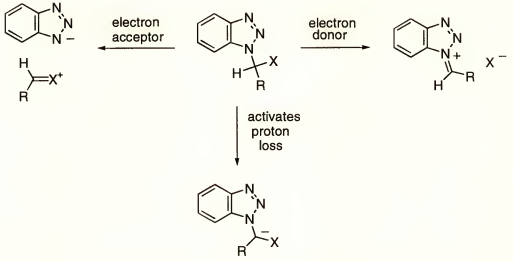


Figure 1.2. Activating Affects of Benzotriazole

1.1 Synthesis of *N*-Substituted Benzotriazoles

Synthetic auxiliaries should be able to be readily introduced into compounds. A number of methods have already been elucidated for the introduction of Bt into various compounds. Methods of synthesizing *N*-substituted benzotriazoles include formation of (1) Bt-C bonds by nucleophilic substitution of a halide, hydroxide or alkoxide moiety, (2) Bt-C bonds by addition to *pi* bonds, and (3) Bt-X bonds, where X = Cl, N, Si, or S, by either redox reactions or nucleophilic substitutions.

1.1.1 Formation of Bt-C Bond by Nucleophilic Substitution

Benzotriazole-carbon bonds have been formed by nucleophilic substitution of halogen, hydroxy or alkoxy groups by a Bt group. Numerous methods have been developed for the nucleophilic displacement of halogens by Bt. Some of the early attempts at such transformations used sodium alkoxides [79HCA2129, 94JMC2754], DMF with NaOH [91RTC369] or heating without base [94H793]. These methods typically give moderate yields of mixtures of Bt^1 and Bt^2 isomers, and occasionally give a quaternary ammonium salt **1.4** by double alkylation (Figure 1.3). More recent attempts at halogen substitution have not employed base, and have given high yields of predominantly the Bt^1 isomer [94S597, 96JHC2031, 95H131]. Substrates utilized include alkyl halides [38CB596, 79HCA2129, 94JMC2754, 70JOC2246], allyl bromide [69JCS(C)1478, 92LA843], *alpha*-bromoacetates [94S597, 96JHC2031], 1,1-diarylalkyl chlorides [96JHC607], and

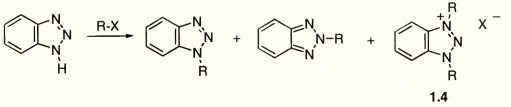


Figure 1.3. Alkylation of Benzotriazole

2- or 4-halopyridines [94S597, 95H131, 93TL2673]. Reactions of BtH with substrates containing more than one halogen will give a mixture of all possible combinations of Bt^1 and Bt^2 isomers, as exemplified by reactions with methylene chloride [83H1787] (Figure 1.4) or chloroform [84OPPI299].

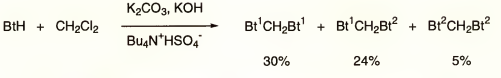


Figure 1.4. Reaction of Benzotriazole With Methylene Chloride

Benzotriazole displaces halide ions from (thio)acyl halides as well as from alkyl halides. Neat heating of BtH with (thio) [73LA636] acyl [92T7817] chlorides gives the corresponding 1-(thio)acylbenzotriazoles in good isolated yields. In the synthesis of *N*-carbamoylbenzotriazoles **1.6**, phosgene is initially reacted in nearly quantitative yield with BtH (1 equiv) to give 1-benzotriazolecarboxylic acid chloride **1.5** (Figure 1.5) [77CCA837]. Reaction of sodium benzotriazolate with cyanogen bromide affords 1-cyanobenzotriazole in 90% yield [91RRC573]. Reaction of secondary amides with sulfinylbisbenzotriazole, prepared *in situ* from thionyl chloride and 1-(trimethylsilyl)benzotriazole, gives imidoylbenzotriazoles in moderate (25 - 62%) yields

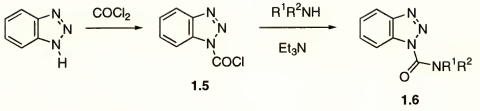


Figure 1.5. Synthesis of *N*-Carbamoylbenzotriazoles

[95H231]. Similarly, the action of BtH, phosphorus oxychloride, and triethylamine on primary, secondary, and tertiary amides gives nitriles **1.9**, enamines **1.8**, and imidoylbenzotriazoles **1.7**, respectively (Figure 1.6) [90CB1545].

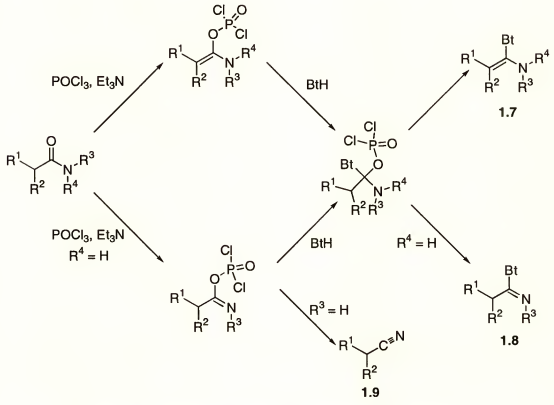


Figure 1.6. Reaction of Amides With BtH, $POCl_3$, and NEt_3

The replacement of a hydroxy or alkoxy group by Bt has also been investigated. The hydroxy group of acids, for example that of formic acid, can be replaced by benzotriazole in the presence of 1,3-dicyclohexylcarbodiimide (DCC) [95S503]. The acid catalyzed reaction of diarylmethanols with BtH, with azeotropic removal of water, gives 1,1-diaryl(benzotriazole)methanes in good yields [90JCS(P2)2059, 96JHC607]. Unactivated alcohols can also be converted into alkylbenzotriazoles, but not directly (Figure 1.7). This transformation is performed by reacting the sodium alkoxide, preformed from the unactivated alcohol, with 1,1'-sulfonyldibenzotriazole to give, *via* an unstable intermediate, a mixture of Bt^1 and Bt^2 isomeric products [93H1253].

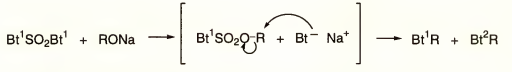


Figure 1.7. Indirect Alkylation of Benzotriazole Using Alcohols

In addition to hydroxyl groups, benzotriazole displaces alkoxy groups in certain types of compounds (Figure 1.8). Dimethoxy ketals give high (65 – 88%) yields of 1-(*alpha*-methoxyalkyl)benzotriazoles **1.10**, which themselves can be further converted into 1-(*alpha*-alkoxyalkyl)benzotriazoles **1.11** by reaction with a different alcohol and simultaneous distillation of the methanol [89JOC6022, 91S279]. Triethyl orthoformate reacts with BtH in fluorocarbon solvent to give a 90% yield of (benzotriazol-1-yl)diethoxymethane (**1.12**). Diethyl acetals undergo similar transformations [95JOC7589, 95JOC7597, 95JOC7612, 95JOC7619]. Both alkoxy groups of an acetal can be replaced by a Bt group if there is a *beta*-carbonyl group, as shown in Figure 1.8 [96SC3773].

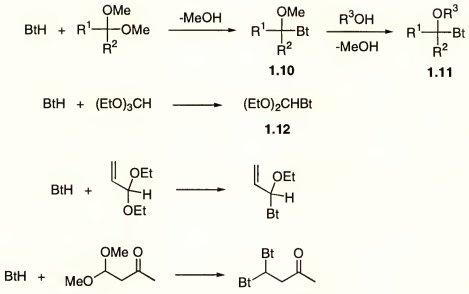


Figure 1.8. Displacement of Alkoxy Groups by Benzotriazole

1.1.2 Formation of Bt-C Bond by Addition to a *Pi* Bond

1.1.2.1 Addition to Olefins

A second method of introducing benzotriazole into compounds is by addition of BtH or an activated Bt-derivative to *pi* bonds, including double or triple bonds between carbon and carbon, nitrogen, oxygen or sulfur. In regards to additions to C-C bonds, Bt-derivatives can add to electron-poor, unactivated and electron-rich olefins. *alpha, beta*-Unsaturated aldehydes, ketones [54JA4933, 92PJC1633], and amides [93JHC1261] undergo Michael addition of BtH in a 1,4-fashion to the exclusion of any 1,2-addition product (Figure 1.9).

Unactivated olefins undergo acid-catalyzed addition of BtH in a sealed tube at 80 °C in moderate yield [95JCS(P2)1645]. These additions give mixtures of Bt^1 and Bt^2

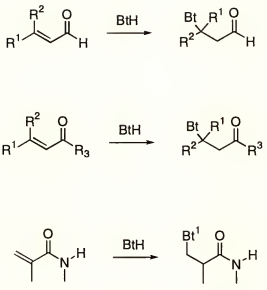


Figure 1.9. Addition of Bt-H to Olefins

isomers as well as positional isomers, when possible, due to rearrangement of the initial carbocation. However, addition of Bt-Cl to unactivated olefins gives good yields of addition products, with regiochemical control (Figure 1.10) [69JCS(C)1478]. Such additions give trans stereochemistry and follow Markovnikov's rule.

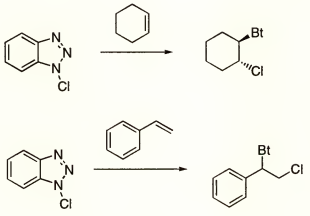


Figure 1.10. Addition of Bt-Cl to Olefins

The addition of BtH to electron-rich olefins, such as enamines, enamides, or vinyl ethers, typically proceeds in excellent yields. For example, addition of BtH across the double bond of *N*-vinylcarbazole (**1.13**), *N*-vinylpyrolidin-2-one (**1.14**) [92S1295], ethyl vinyl ether (**1.15**), and 2,3-dihydrofuran (**1.16**) [90JCS(P1)1717] is illustrated in Figure 1.11.

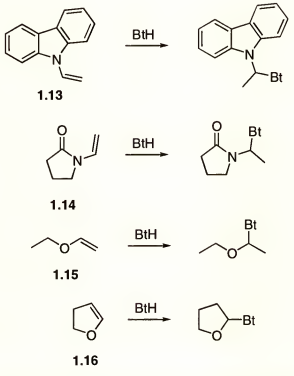


Figure 1.11. Addition of Bt-H to Activated Olefins

1.1.2.2 Addition to Imines, Iminium Cations, and Nitriles

Addition of BtH to imines or iminium cations is a highly efficient way to form Bt-C bonds. A common method for such reactions is to react a carbonyl compound, BtH, and an amine under dehydrating conditions to give *N*-(*alpha*-aminoalkyl)benzotriazoles.

For example, when ammonia is used as the amine (Figure 1.12), aliphatic aldehydes give bis(1-benzotriazol-1-ylalkyl)amines **1.17** and aromatic aldehydes give (1-benzotriazol-1-ylalkyl)-*N*-alkylideneamines **1.18** [91S703].

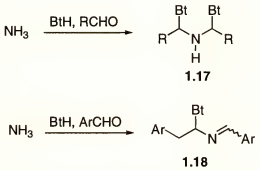


Figure 1.12. Synthesis of *N*-(*alpha*-Aminoalkyl)benzotriazoles Using Ammonia

Unlike those with ammonia, reactions of primary amines require precise conditions. The use of equimolar amounts of BtH, hindered aliphatic primary amine and aldehyde [90CB1443, 90JCS(P1)541] or ketone [89S66] gives good (85 – 100%) yields of mono-adducts **1.19** (Figure 1.13). When 2 equiv of both BtH and formaldehyde are reacted with such amines, good (62 – 92%) yields of bis-adducts **1.20** are formed [87JCS(P1)799, 90JCS(P1)541]. The use of equimolar amounts of primary amine and BtH with an excess of formaldehyde affords good yields (65 – 99%) of products of type **1.21** [90JCS(P1)541]. Except when formaldehyde is used, primary aromatic amines only give monoadducts with carbonyl compounds [90S1173, 90RTC337, 89JHC1579, 87JCS(P1)799, 89OPPI340, 90CJC446].

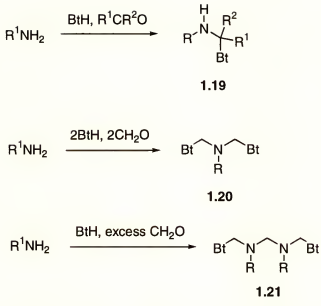


Figure 1.13. Synthesis of *N*-(*alpha*-Aminoalkyl)benzotriazoles Using Primary Amines

In addition to imines and imonium cations derived from ammonia and primary amines, BtH has also been reacted with such entities derived from secondary amines. Reaction of various secondary amines with aldehydes [89JCS(P1)225, 89OPPI135, 90S1173, 89S323, 90JCS(P1)667] or ketones [89S66] and BtH furnished good to excellent yields of adducts of type **1.22** (Figure 1.14). Dialdehydes react smoothly with BtH (2 equiv) and amine (2 equiv) to give compounds of type **1.23** [90JOC3209]. Primary diamines react with formaldehyde and BtH to give an adduct at each free *N*-H [96JOC7585]. Other successful condensations have occurred when hydroxylamines [89JCS(P1)225, 87JCS(P1)799, 90JCS(P1)541], amides [88JCS(P1)2339, 93JOC2086, 90JOC2206], thioamides [88TL1755, 91JCS(P1)2199], sulfonamides [89CS27, 97SC907], and hydroxamic acids [90S663] have been utilized instead of amines.

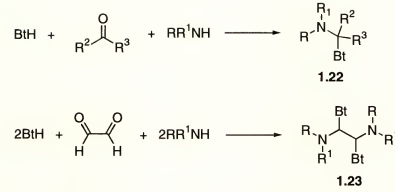


Figure 1.14. Synthesis of *N*-(*alpha*-Aminoalkyl)benzotriazoles Using Secondary Amines

Only a few examples of BtH addition to C-N triple bonds have been reported. Among these are the addition of BtH in the presence of *p*-toluenesulfonic acid to cyanamide [95SC1173] to give benzotriazole-1-carboxamidinium tosylate in 77% yield and the reaction of an excess of BtH to cyanogen bromide to give dibenzotriazol-1-ylmethylimine [96MI4011] in 80% yield (Figure 1.15).

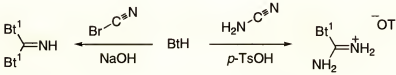
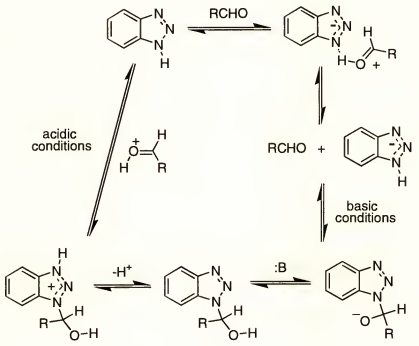


Figure 1.15. Addition of Bt-H to C-N Triple Bonds

1.1.2.3 Addition to a (Thio)Carbonyl Group

Benzotriazole adds to aliphatic aldehydes [87JCS(P1)791, 96SC3773] or dialdehydes [90JHC1543] to give crystalline compounds of type **1.24**. These reactions

proceed under acidic or basic conditions, as shown in Figure 1.16. Unlike their aliphatic counterparts, aromatic aldehydes do not react directly with BtH. Aliphatic and aromatic



1.24

Figure 1.16. Addition of Bt-H to Aldehydes

aldehydes undergo condensation reactions with alcohols and BtH to give 1-(1-alkoxyalkyl)benzotriazoles in good (51 – 82%) yields [95JOC7619, 96JOC4035]. Electrophilic attack of intermediate cation **1.25** on BtH followed by deprotonation gives the final product (Figure 1.17).

Benzotriazole adds to thiooxonium cations as well as to oxonium cations. The reaction of thiols with carbonyl compounds is believed to follow the mechanism depicted in Figure 1.18. Addition of thiol to aldehyde gives, after loss of water, intermediate **1.26** containing a $C{=}S^{+}R$ moiety. Subsequent addition of BtH gives Bt^{1}/Bt^{2} mixtures as

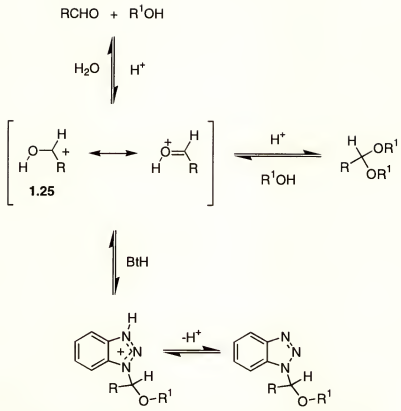


Figure 1.17. Reaction of Bt-H, Alcohols, and Aldehydes

products, each compound of which can be separated by chromatography. These reactions proceed with aliphatic or aromatic aldehydes as well as some ketones [89CS27, 91HCA1924], namely acetone, cyclopentanone, cyclohexanone, and cycloheptanone.

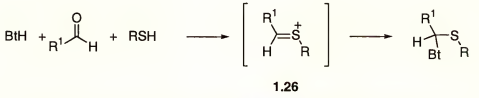


Figure 1.18. Reaction of Bt-H With Thiooxonium Intermediates

1.1.3 Formation of a Bt-X Bond by Redox Reaction or Nucleophilic Substitution

A third method of introducing Bt into compounds is by formation of Bt-X bonds, where X = Cl, Si, N, or S (Figure 1.19). 1-Chlorobenzotriazole is rapidly and quantitatively formed when bleach (sodium hypochlorite solution) is added to BtH in a 50% aqueous acetic acid solution [69JCS(C)1474]. 1-(Trimethylsilyl)benzotriazole, which is air sensitive, is readily collected by distillation from a mixture of BtH and hexamethyldisilazane [80JOM141]. Reaction of BtH with hydroxylamine-*O*-sulfonic acid in aqueous KOH solution gives a Bt^1/Bt^2 mixture of *N*-aminobenzotriazole [69JCS(C)742]. 1-(Trimethylsilyl)benzotriazole (2 equiv) reacts with sulfur chlorides to give quantitative yields of the corresponding 1,1'-thio- and 1,1'-dithiobisbenzotriazoles [78JA1222].

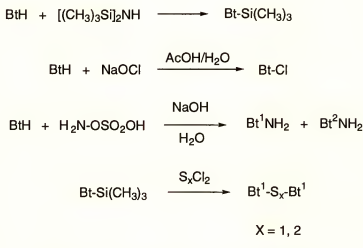


Figure 1.19. Formation of Various Bt-X Bonds

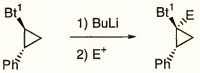
1.2 Reactions of *N*-Substituted Benzotriazoles

Intermediates that contain Bt, shown in the above section to be easily synthesized, undergo a variety of reactions without the loss of the Bt moiety. These reactions can be grouped into three categories: (1) deprotonation followed by reaction with electrophile or rearrangement, (2) substitution, or (3) addition of Bt-C-X to olefins.

1.2.1 Deprotonation *alpha* to a Benzotriazolyl Group

Methods which deprotonated a hydrogen *alpha* to a heteroatom was well-known even 30 years ago [69CRV639], and the chemistry of BtH takes advantage of this facile deprotonation. Such deprotonations have been performed on a multitude of systems, including alkyl-, vinyl-, allyl-, and benzylbenzotriazoles as well as Bt-CH-X systems (X = N, O, S, P, Si), but only the alkyl, vinyl, allyl, and Bt-CH-N systems will be discussed here.

Alkylbenzotriazoles [94LA1], including 1-methyl-, 1-ethyl-, and 1-propyl-benzotriazole, have been lithiated and further reacted with electrophiles to give *N*-(*alpha*-substituted alkyl)benzotriazoles. Benzotriazole is a relatively strong activator, and the anion of compound **1.27** alkylates *alpha* to the benzotriazolyl group to the exclusion of the benzyl position (Figure 1.20) [95JHC595].



1.27

Figure 1.20. Lithiation/Alkylation of an Alkylbenzotriazole

Vinylbenzotriazoles also undergo *alpha*-lithiation and subsequent reaction with various electrophiles [92LA843, 90HAC21]. When the *alpha* position of a vinylbenzotriazole is already substituted, lithiation does occur at the *beta* position and addition of electrophile gives products with E stereochemistry, presumably due to coordination of lithium to N2 of the Bt moiety (Figure 1.21) [94T6005].

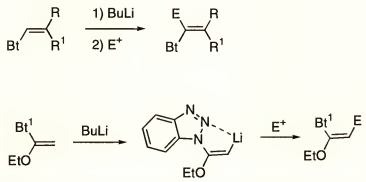
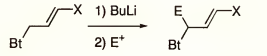


Figure 1.21. Lithiation/Alkylation of Vinylbenzotriazoles

Lithiation/alkylation sequences performed on allylbenzotriazoles give products of *alpha*-alkylation. This regiochemical control is observed when the *gamma* position is substituted by an -H, -R [92LA843], -NR_2 [95TL343, 96SC1385], -OEt [95S1315], or $OSi(CH_3)_3$ group (Figure 1.22).

Benzotriazol-1-ylmethyl isocyanide gives moderate yields of alkylated derivatives when sequentially treated with potassium *tert*-butoxide and alkyl halide (Figure 1.22) [96H67]. *N*-(Benzotriazolylmethyl)heterocycles, namely pyrrole [89JHC829], indole [95OM734, 89JHC829, 93T2829], carbazole [95OM734, 89JHC829, 91JOC2143, 91JOC6917, 93JOC1970, 94JOC5097], and benzotriazole [52JA3868, 87JCS(P1)819], undergo lithiation and alkylation *alpha* to Bt. However, 1,2,4-triazol-1-yl-, benzimidazol-

1-yl-, and imidazol-1-yl-substituted methylbenzotriazoles give products from heteroring-alkylation as well as *alpha*-alkylation [89JHC829].



X = H, R, NR_2, OEt, OTMS

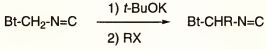


Figure 1.22. Selected Deprotonations/Alkylations of Alkylbenzotriazoles

Treatment of 1-allylbenzotriazole with potassium *tert*-butoxide induces isomerization into a 5:1 mixture of (*E*)- and (*Z*)-(benzotriazol-1-yl)propene in 90% yield (Figure 1.23) [69JCS(C)1478]. 2-Allylbenzotriazole under similar conditions gives a 4:1 ratio of the corresponding (*E*)- and (*Z*)-(benzotriazol-2-yl)propene in 85% yield [92LA843]. Neither the Bt^1/Bt^2 isomers nor the cis/trans isomers interconvert upon heating.

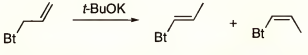


Figure 1.23. Isomerization of 1-Allylbenzotriazole

1.2.2 Substitutive Benzotriazolylalkylation

A second category of reactions of Bt-derivatives in which the Bt group is retained is substitutive benzotriazolylalkylation. Most of these reactions involve either 1-(*alpha*-chloroalkyl)- **1.28** or 1(*alpha*-hydroxyalkyl)-benzotriazoles **1.29** (Figure 1.24). The chloro compounds **1.28** are obtained from the corresponding hydroxy compounds **1.29** by reaction with thionyl chloride [52JA3868, 87JCS(P1)811].

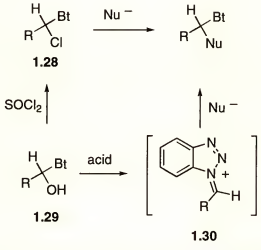


Figure 1.24. Substitutive Benzotriazolylalkylation

Nucleophilic displacement of chloride from compounds **1.28** is quite facile [87JCS(P1)781]. Nucleophiles utilized in this type of reaction include carbon, nitrogen, oxygen, sulfur and phosphorus compounds.

The cation **1.30**, generated *in situ* from **1.29** by a catalytic amount of Lewis acid, undergoes electrophilic attack on a multitude of electron-rich compounds, including a variety of aromatics. The benzotriazolylmethylation of aniline derivatives gives *para*-

substitution [93T7445, 90S341], of phenols gives *ortho*-substitution [91CB1809], of phenol ethers gives a mixture of *ortho*- and *para*- substitution [93PJC1243, 91CB1809], and of substituted arenes gives all positional isomers [92JCS(P1)1111]. The reaction of compound **1.31** with boron trifluoride etherate followed by a methyl ketone affords monosubstituted compound **1.32** (Figure 1.25) [94JHC917]. Dialkyl ketones under the same conditions give mixtures of *alpha*-mono- and *alpha*, *alpha*-di-substituted products.

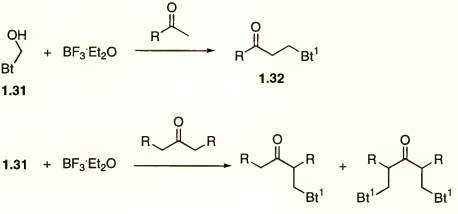


Figure 1.25. Benzotriazolylmethylation

1.2.3 Additive Benzotriazolylalkylation

The third important category of reactions of Bt-compounds in which the Bt group is in the product is additive benzotriazolylalkylation. Most of these additions involve the attack of *in situ* generated iminium or oxonium ions to an activated double bond, such as enamines, enamides, or vinyl ethers. However, as mentioned in the previous section, Bt-Cl also adds across activated double bonds in a Markovnikov fashion [95H131].

1-(*alpha*-Aminoalkyl)benzotriazoles **1.33** are readily prepared precursors for iminium benzotriazolides. In solution, compounds **1.33** dissociate in an equilibrium-controlled fashion into an iminium cation **1.34** and a Bt anion (Figure 1.26). The Bt anion can then attack cation **1.34** from either N2 or N1 to give the corresponding Bt^2 and Bt^1 compounds; thus, Bt^1/Bt^2 isomerization is usually unavoidable in solution for this type of compound.

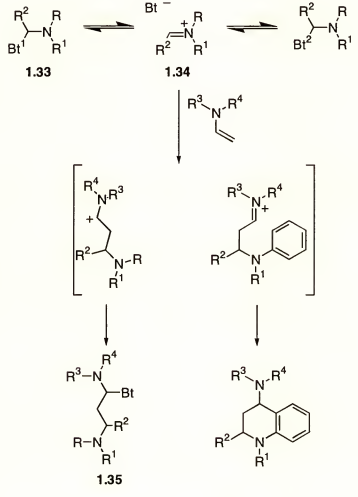


Figure 1.26. Reaction of an Enamine With an Iminium Benzotriazolide

When treated with an enamine or enamide, cation **1.34** adds *beta* to the nitrogen of the enamine or enamide, and the Bt anion subsequently attacks the *alpha* position to give compounds of type **1.35** [94JOC5206, 96JOC7558, 93JOC1970, 93JOC812]. When compounds **1.33** are aniline derivatives, products **1.35** are not isolated. Instead, the intermediate cation undergoes intramolecular attack at the *ortho* position of the aniline ring to give 4-amino-1,2,3,4-tetrahydroquinolines [95JOC3993]. This methodology has been applied to the synthesis of *N*-aminopropyl-substituted lariat crown ethers [96JOC7558, 96JOC7585] and julolidines (Figure 1.27) [96JOC3117].

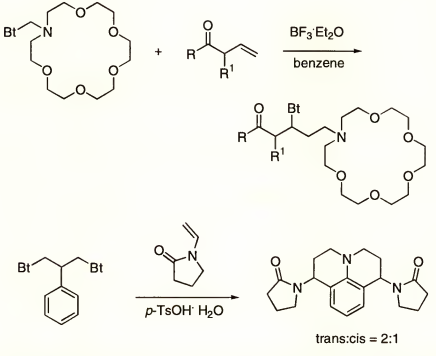


Figure 1.27. Synthesis of *N*-Aminopropyl-Substituted Lariat Crown Ether and Julolidine

Such iminium cations also react with ethyl vinyl ethers [96JOC7578, 92JOC4932, 93JOC4049]. When the *N*-(*alpha*-aminoalkyl)benzotriazole is derived from an aldehyde

other than formaldehyde and the enol ether is 2,3-dihydrofuran, a multitude of isomers is obtained since the products will consist of Bt^1/Bt^2 isomers that have three diastereocenters (Figure 1.28) [95JOC2588]. Paralleling the reactions with enamines, lariat crown ethers [96JOC7585], 1,2,3,4-tetrahydroquinolines [95JOC2588], and julolidines [96JOC3117] have been synthesized from enol ethers. However, since both Bt and ethoxy groups are good leaving groups, the crude product contains a mixture of Bt-substituted 1,2,3,4-tetrahydroquinoline **1.36** and ethoxy-substituted 1,2,3,4-tetrahydroquinoline **1.37** products; the uncyclized aniline derivative is also occasionally obtained (Figure 1.29).

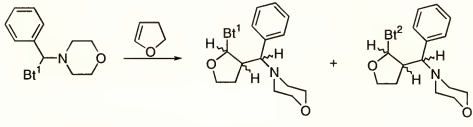


Figure 1.28. Products From 2,3-Dihydrofuran

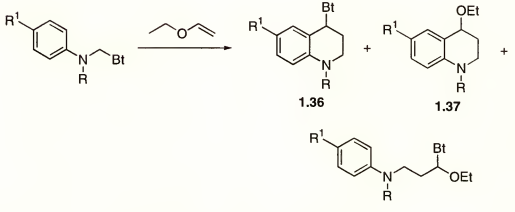
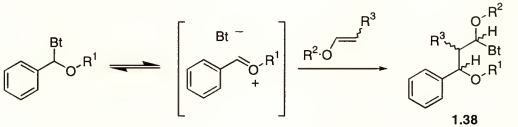


Figure 1.29. Products From Ethyl Vinyl Ether

Similar to their amino-analogs, 1-(*alpha*-alkoxybenzyl)benzotriazoles react with enol ethers [92JOC4925] *via* oxonium benzotriazolides to give products **1.38** (Figure 1.30).



1.38

Figure 1.30. Reaction of 1-(alpha-Alkoxybenzyl)benzotriazoles With Enol Ethers

1.3 Removal of Benzotriazole From *N*-Substituted Benzotriazoles

A good synthetic auxiliary should be easily removable. Benzotriazole has been removed from compounds by nucleophilic substitution, elimination, hydrolysis, cyclization, and reduction [98CRV409]. Only selected nucleophilic substitutions and eliminations will be discussed herein.

1.3.1 Nucleophilic Substitution of Benzotriazole

Nucleophilic substitution of Bt has been accomplished with a multitude of nucleophiles including H-, C-, N- [94JCS(P2)1867, 96JHC1935], O-, S-, Se- [93S229], P [93JOC1987, 94JOC4556], and Sn- [94S904, 94S907] nucleophiles; only the use of H- and C- nucleophiles will be addressed herein. The use of such nucleophiles on Bt-C-N systems provides access to a multitude of symmetrical and unsymmetrical primary,

secondary, and tertiary amines. Sodium borohydride [89JCS(P1)225, 91MI33] and $LiAlH_4$ [96JOC7578, 96JOC7585] are the H- nucleophiles typically utilized, while the C-nucleophiles include Grignard [89JCS(P1)225, 96JHC1935, 90CJC456, 91MI33, 90CB1443], organozinc [96JOC7585, 89S323], organosamarium [96SC3395], organobismuth [91TL4247, 92OM1381], organolithium [91S703, 89JCS(P1)2297], and Reformatsky-type [96JOC7585, 34JA697, 64G37] reagents, depending upon the functional groups present in the substrate and the desired product. Such reactions are generalized in Figure 1.31.

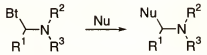


Figure 1.31. Nucleophilic Substitution of Benzotriazole

1.3.2 Elimination of Benzotriazole

Reactions in which Bt is eliminated provide a method for introducing a new double bond into a compound. So far, double bonds formed using this methodology include C=C, C=N [93S233, 94JCS(P1)113], and C=O [89JCS(P1)639], of which only the first will be discussed herein.

The formation of a C=C bond is believed to proceed through an initial ionization step followed by base-promoted deprotonation, as depicted in Figure 1.32 for the synthesis of enamines from *N*-(*alpha*-aminoalkyl)benzotriazoles. In solution, the starting material undergoes reversible ionization, but subsequent deprotonation by sodium

hydride yields enamines [90T8153], enamides [92OPPI475], and enol ethers [91S279]. This methodology was extended to the synthesis of dienamines [91TL3597].

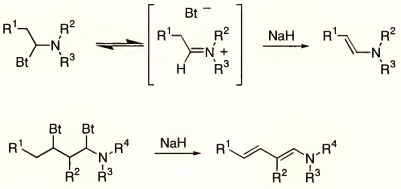


Figure 1.32. Elimination of Benzotriazole

This introduction provided a brief overview of methodology that employs benzotriazole-derivatives as it relates to the synthesis and utility of selected *N*-substituted benzotriazoles. The aforementioned reactions provide the essential background for Chapters 2-5, which describe the syntheses of *beta*-amino esters (Chapter 2) and of 1,2,3,4-tetrahydroquinolines (Chapter 3) *via N*-(*alpha*-aminoalkyl)benzotriazoles and the synthesis and utility of 1-benzotriazolylenamines (Chapter 4) and of 1-benzotriazolyl-3-phenylsulfonylprop-1-ene (Chapter 5).

CHAPTER 2
SYNTHESIS OF *ALPHA*-FLUORINATED *BETA*-AMINO ESTERS *VIA N*-(*ALPHA*-AMINOALKYL)BENZOTRIAZOLES

2.1 Introduction

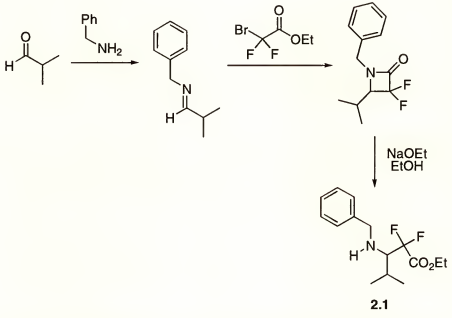
Replacement of hydrogen with fluorine in organic molecules frequently enhances the bioactivity of such compounds [97JCS(CC)645]. This increased bioactivity is attributed to the combination of the similar geometry of the fluorinated compounds in comparison with their hydrogen analogs, the opposite polarization of the C-F bond with respect to the C-H bond, and the greater bond dissociation energy of the C-F bond over that of the C-H bond ($\Delta\Delta H$ = 17 kJ/mol) [95MI1]. Although the steric bulk of the fluorine atom (van der Walls radius = 1.47 Å) being similar to that of the hydrogen atom (van der Walls radii = 1.2 Å) is debated, the binding of fluorine analogs to target proteins does not usually show any sign of steric hindrance in comparison with their hydrogen models [97JCS(CC)645].

Because of the increased propensity of fluorinated compounds to have greater bioactivity than their non-fluorinated analogs, the pharmaceutical and agrochemical industries, as well as academia, have great interest in the development of the chemistry of fluorinated compounds. Evidence of the interest in the field of fluorinated amino acids lies in the results from a search of the science citation index from January 1990 through June 1999 which generated 166 references to titles that contain simultaneously the three

words "fluorinated", "amino", and "acid". This abundance of literature relating to fluorinated amino acids is due to the still unrealized potential of these compounds in medicinal chemistry [95MI1, 98JOC1878]. Since non-fluorinated *beta*-amino acids have been shown to be essential functional units in naturally occurring antibiotics and peptides, as well as being building blocks for synthetic 2-azetidinones and peptides [98JOC1878], it comes as no surprise that fluorinated *beta*-amino acids have become a synthetic target for scientists [95MI1, 98JOC1878, 92MI1235]. Peet and co-workers at Dow Chemicals synthesized a peptidyl 2,2-difluoro-3-aminopropanoate in the unrealized hope that it would inhibit human neutrophil elastase and they indicated that peptides containing *alpha*, *alpha*-difluoro-*beta*-amino esters might be useful as inhibitors of other proteolytic enzymes [92MI1235].

Despite this apparent interest in fluorinated *beta*-amino esters, only a single example has been described of the synthesis of an *alpha*, *alpha*-difluoro-*beta*-amino ester. This is ethyl 3-(benzylamino)-2,2-difluoro-4-methylpentanoate (**2.1**) formed by a Reformatsky reaction with an iminium cation precursor (Figure 2.1) [92MI1235]. This synthesis gave only a 6% yield of the ester. The major product in 73% yield was the corresponding 1-benzyl-2,2-difluoro-3-isopropyl-2-azetidinone; the azetidinone was subsequently converted in 80% yield into the ester for an overall 2-step yield of 64%. The lack of literature procedures for the synthesis of *alpha*, *alpha*-difluoro-*beta*-amino esters is not due to a lack of efforts, since previous syntheses of 2,2-difluoro-2-azetidinones from Reformatsky reaction with imines [88TL5291, 92MI1235], ketene-imine condensations [91TL5461, 93JOC2454], or enolate-imine condensations [91TL5461, 92TL7903, 93JOC2302] have been quite successful. However, even for the

aforementioned synthesis of ethyl 3-(benzylamino)-2,2-difluoro-4-methylpentanoate (**2.1**), these methods are apparently not easily modified to allow for the isolation of the corresponding *alpha*, *alpha*-difluoro-*beta*-amino esters directly, and require an additional chemical transformation in order to gain access to these esters.



2.1

Figure 2.1. Synthesis of an *alpha*, *alpha*-Difluoro-*beta*-Amino Ester

Moreover, only one paper has been published on the synthesis of 2-monofluoro-*beta*-lactams; this publication contained 5 examples of products obtained from a four-step procedure in a 17-30% overall yield (Figure 2.2) [96T255]. A comprehensive literature search did not reveal even one synthesis of an *alpha*-monofluoro-*beta*-amino ester or that of an *alpha*-fluorinated bis(*beta*-amino ester).

This investigation will now demonstrate that Reformatsky reactions of mono- and di-fluorobromoacetates with *N*-(*alpha*-aminoalkyl)benzotriazoles used as iminium salt

precursors provide a general and efficient route to *alpha*-mono- and *alpha*, *alpha*-difluoro-*beta*-amino esters and *alpha*-mono- and *alpha*, *alpha*-difluoro-bis(*beta*-amino esters).

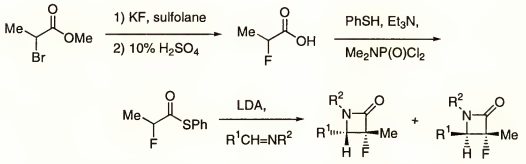


Figure 2.2. Synthesis of a Monofluorinated Azetidinone

2.2 Results and Discussion

The current investigation was undertaken because of the apparent lack of an efficient way to prepare *alpha*-fluorinated *beta*-amino esters, which have great potential in the pharmaceutical industry. It is known that *N*-(*alpha*-aminoalkyl)benzotriazoles are readily prepared from BtH, aldehyde and amine [91T2683, 94AA31, 94CSR363, 94S445], and that a Reformatsky-type reaction successfully displaced both Bt moieties from *N,N'*-bis(benzotriazolylmethyl)-4,13-diaza-18-crown-6 [96JOC7585]. The goal of this investigation was therefore to use benzotriazole methodology to efficiently synthesize *alpha*-mono- and *alpha*, *alpha*-difluoro-*beta*-amino esters from a Reformatsky-type reaction of bromofluoroacetates with *N*-(*alpha*-aminoalkyl)benzotriazoles. The aim was to synthesize such *beta*-amino esters with primary, secondary, or tertiary amino groups and the *alpha* carbon having an alkyl

substituent. An additional goal was to explore the possibility of synthesizing *alpha*-mono- and *alpha*, *alpha*-difluoro-bis(*beta*-amino esters).

2.2.1 Attempts to Synthesize *N*-(*alpha*-Aminoalkyl)benzotriazoles **2.2a-g**

The Bt-containing intermediates used toward the synthesis of *alpha*-fluorinated *beta*-amino esters were *N*-(*alpha*-aminoalkyl)benzotriazoles **2.2a-g**. This type of compound has been synthesized by aminomethylation (Mannich reaction) of benzotriazole with aldehydes or ketones and either ammonia, arylamines, or dialkylamines [98CRV409]. There are multiple potential mechanistic pathways that might be followed for such condensations, as shown in Figure 2.3. Secondary amines probably undergo initial condensation with the carbonyl compound to give the iminium cation intermediate and subsequent reaction with BtH to give the *N*-(*alpha*-aminoalkyl)benzotriazole. Similarly, primary amines are believed to give imines by reaction with aldehyde or ketone, and subsequent addition of BtH across the imine's double bond affords the isolated product. Alternatively, BtH could react with the carbonyl group to give an alcohol which would condense with amine to give the *N*-(*alpha*-aminoalkyl)benzotriazole. In addition to their vast utility as synthetic intermediates, some *N*-(*alpha*-aminoalkyl)benzotriazoles are also used as additives in corrosion inhibitors, in lubricating and insulating oils and in photopolymerizable paints [87JCS(P1)799].

Except for **2.2e**, syntheses of the *N*-(*alpha*-aminoalkyl)benzotriazoles, **2.2a** [75JCS(P1)1181], **b** [87JCS(P1)799], **c** [89OPPI135], **d** [95JOC3993], **f** [94CJC1849]

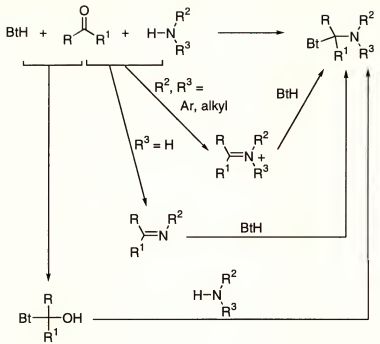
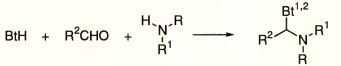


Figure 2.3. Mechanism for Formation of *N*-(*alpha*-Aminoalkyl)benzotriazoles

and **g** [98JOC6712], have been previously published. Various methods have been utilized to synthesize such compounds, including reaction of (1) varied ratios of aldehyde, BtH and amine in (1.1) diethyl ether with and without molecular sieves, (1.2) refluxing in ethanol, (1.3) refluxing in toluene with azeotropic removal of water, or (1.4) in water, and (2) 1-(hydroxymethyl)benzotriazole with amine. In the current work, each of these compounds, both the monocondensation type **2.2a-e** (Figure 2.4) and the biscondensation type **2.2f,g** (Figure 2.5), were synthesized by refluxing in toluene a mixture of one equivalent (equiv) of BtH and aldehyde for each mole of nitrogen in the amine. Progress of these reactions, which never took more than 2 hours (h) to complete, was monitored by the amount of water collected in the attached Dean-Stark trap. Compounds were then obtained, after removal of volatiles, by crystallization from diethyl ether. Compound **2.2e**

could not be purified by crystallization or column chromatography, and was therefore used directly in the next step without further purification.



2.2	R	R^1	R^2
a	Me	Ph	H
b	Ph	Ph	H
c	H	Ph	H
d	Ph	Me	*i*-Pr
e	$PhCH_2$	$PhCH_2$	$Ph(CH_2)_2$

Figure 2.4. Synthesis of *N*-(*alpha*-Aminoalkyl)benzotriazoles

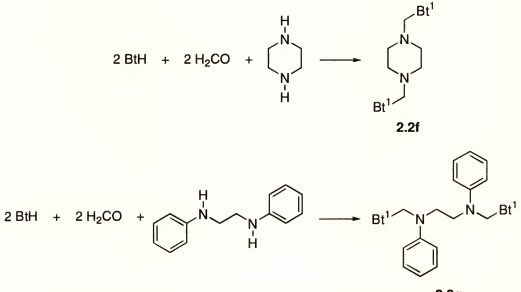


Figure 2.5. Synthesis of Bis[*N*-(*alpha*-aminoalkyl)benzotriazoles]

Although the above procedure worked for all of the aforementioned *N*-(*alpha*-aminoalkyl)benzotriazoles, milder conditions gave superior yields for compounds **2.2b-d**.

Compound **2.2b** was best synthesized by refluxing in absolute ethanol an equimolar mixture of *N*-phenylaniline, BtH, and 37% aqueous formaldehyde for 16 h; pure compound was obtained by removal of volatiles followed by crystallization from diethyl ether. When equimolar amounts of aniline, BtH, and 37% aqueous formaldehyde were stirred at room temperature (rt) for 2 h, compound **2.2c** crystallized out of solution and was analytically pure after vacuum filtration. Compound **2.2d** was synthesized by shaking a mixture of *N*-methylaniline, isobutyraldehyde (1.2 equiv), BtH (1.0 equiv), *p*-toluenesulfonic acid monohydrate (0.025 equiv), 4Å molecular, sieves and diethyl ether for 1 h. Pure compound was isolated by filtration, removal of volatiles, and subsequent crystallization from diethyl ether. An attempt to make the condensation product from equimolar amounts of *N,N*-dibenzylamine, BtH, and phenylacetaldehyde by stirring the mixture for 4 h in ethanol gave an analytically pure sample of 1-dibenzylamino-2-phenylethylene (**2.3**) in 85% yield by simple filtration of the formed precipitate. Compound **2.3** was not converted to the desired intermediate of type **2.1** by refluxing with a five-fold excess of BtH in THF for 2 d (Figure 2.6).

Structures for compounds **2.2a-d,f,g** were assigned by comparison of their NMR spectra with those found in the literature. In addition to having a satisfactory elemental analysis, compound **2.3** gave NMR spectra consistant with the proposed structure. The ^{1}H NMR showed a 16-proton multiplet (15 from the benzene rings and 1 from a vinylic proton) from 7.35-6.96 ppm, a 1-proton doublet at 5.33 ppm having a 14.0 Hz coupling constant indicative of a trans orientation with another vinylic proton, and a 4-proton singlet (4.30 ppm) for the benzylic protons. The ^{13}C NMR spectrum contained a number

of aromatic peaks in addition to signals at 98.3 and 54.7 ppm that correspond to C1 and the benzylic carbons, respectively.

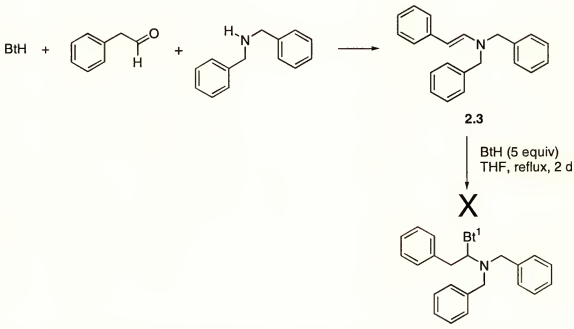
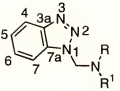


Figure 2.6. Condensation of Dibenzylamine, Penylacetaldehyde, and Bt-H

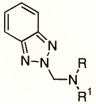
Unlike compounds **2.2f,g** that only have Bt^1 moieties, the *N*-(*alpha*-aminoalkyl)benzotriazoles **2.2a-e** were isolated as mixtures of benzotriazol-1-yl and benzotriazol-2-yl isomers. It has been shown that this type of compound forms an equilibrium between the Bt^1 and Bt^2 isomers in solution *via* dissociation into a Bt anion and an iminium cation and subsequent recombination with nucleophilic attack from either the 1 or 2 position of the Bt anion [87JCS(P1)2673]. Thus, these compounds are well suited for use as iminium salt precursors [98CRV409].

The ratio between the Bt^1 and Bt^2 isomers in a given solvent is usually easily determined by ^1H NMR spectroscopy experiments [87JCS(P1)2673, 87JCS(P1)799]. For

any one Bt^1/Bt^2 mixture, the Bt^2 compound has a C2 plane of symmetry which runs through N2 and between C5 and C6; thus, the Bt^2 moiety shows a simple AA'BB' splitting pattern with the C4 and C7 protons deshielded to about δ_H 7.9 ppm by the lone electron pairs on N1 and N3, respectively. The Bt^1 isomer shows distinct peaks for each of the four aromatic protons, with only the C4 proton being deshielded to about δ_H 8.0 ppm by the lone electron pair on N1. Thus, integration of the 2 deshielded protons of the Bt^2 isomer can be compared to that for the single proton of the Bt^1 isomer to give a close approximation of the isomeric ratio; typically, the Bt^1/Bt^2 ratio is close to 2. Occasionally, it is also possible to determine the isomeric ratio by integration of the signals for the protons attached to the aliphatic carbon attached between the Bt group and the amino functionality (δ_H 5.5 ppm). However, even though this proton for the Bt^2 isomer is typically more deshielded than that for the Bt^1 isomer, signal overlap usually makes accurate integration of the two peaks untenable. As can be seen in Figure 2.7, there are also differences between the Bt^1 and Bt^2 isomers in the ^{13}C NMR spectra [90JCS(P1)541]. The Bt^1 isomers typically give signals for the quaternary carbons at δ_C 146 (C3a) and 132 (C7a) ppm, for the CH carbons at δ_C 120 (C4), 124 (C5), 127 (C6), and 110 (C7) ppm, and for the NCN carbon at δ_C 64 ppm. The carbons for the Bt^2 isomers show at δ_C 144 (C3a/C7a) ppm, δ_C 126 (C4/C7) ppm, δ_C 118 ppm (C5/C6), and δ_C 67 (NCN) ppm.



	C3a	C4	C5	C6	C7	C7a	NCN
^{13}C (ppm)	145.4-147.8	118.9-120.1	123.5-124.2	126.7-127.6	109.2-111.1	132.0-132.8	58.6-63.7



	C3a/C7a	C4/C7	C5/C6	NCN
^{13}C (ppm)	143.1-144.5	126.0-126.3	117.9-119.1	66.3-71.8

Figure 2.7. Typical NMR Data for *N*-(*alpha*-Aminoalkyl)benzotriazoles

2.2.2 Reformatsky Reagents

The other reagents used in the current synthesis of *alpha*-fluorinated *beta*-amino esters were Reformatsky reagents. These reagents, generated *in situ* from the reaction of zinc with *alpha*-bromoacetates, have previously been successfully utilized in reaction with imines to give 2-azetidinones; it was also shown that a catalytic amount of trimethylchlorosilane added to the zinc before addition of the ester improves yields [89JCS(CC)74]. Therefore, the Reformatsky reagents used in the current study were preformed. Stirring a mixture of THF, zinc dust and trimethylchlorosilane (0.40 equiv) for 10 minutes (min) at rt, adding either the ethyl bromodifluoroacetate or ethyl

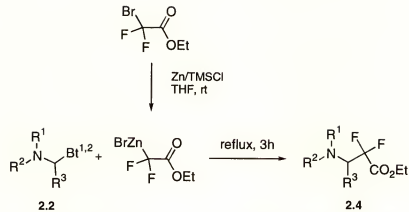
bromofluoroacetate, and stirring for an additional 10 min at rt provided a reagent ready for use.

2.2.3 Reaction of *N*-(*alpha*-Aminoalkyl)benzotriazoles **2.2a-g** With Reformatsky Reagents

The final step in this method's synthesis of *alpha*-fluorinated *beta*-amino esters was the formal replacement of each Bt moiety from the *N*-(*alpha*-aminoalkyl)benzotriazole intermediate with an ethyl *alpha*-fluorinated acetate moiety. This step proceeded *via* nucleophilic attack by the *in situ* generated Reformatsky reagent on the iminium cation. This was accomplished by adding the Bt-containing intermediate (5 mmol) to the solution containing the Reformatsky reagent (1.5 equiv), and refluxing the mixture for 3 h. After work-up as described in the experimental section, compounds **2.4a-e**, **2.5a-c**, and **2.6a-d** were isolated in pure form by flash column chromatography (10:1 hexanes:ethyl acetate) of the crude product. Structure elucidation for compounds **2.4a-f**, **2.5a-c** and **2.6a-d** will be discussed prior to the experimental section.

2.2.4 Ethyl *alpha*, *alpha*-Difluoro-*beta*-amino Esters **2.4a-f**

When bromodifluoroacetate was used as the Reformatsky precursor in reaction with the iminium cation derived from *N*-(*alpha*-aminoalkyl)benzotriazoles, ethyl *alpha*, *alpha*-difluoro-*beta*-amino esters **2.4a-e** were synthesized in excellent yields (Figure 2.8, Table 2.1). This constitutes the assembly of a difluoroacetate, an aldehyde and an amine in a two-step procedure. The amine can either be an aniline derivative, aniline for compound



2.2 **2.4**

Figure 2.8. Synthesis of *alpha*, *alpha*-Difluoro-*beta*-Amino Esters

Table 2.1. Selected Data for Identification of *alpha*, *alpha*-Difluoro-*beta*-amino Esters **2.4a-e**

Product	**2.4a**	**2.4b**	**2.4c**	**2.4d**	**2.4e**
R^1	Ph	Ph	Ph	Ph	CH_2Ph
R^2	Me	Ph	H	Me	CH_2Ph
R^3	H	H	H	*i*-Pr	$(CH_2)_2Ph$
Yield (%)	90	87	92	89	80
mp (°C)	oil	oil	oil	52-54	oil
C1[a]	163.5 (t)	163.5 (t)	163.5 (t)	163.8 (t)	163.9 (t)
C2[a]	114.9 (t)	114.2 (t)	114.4 (t)	117.5 (t)	118.4 (t)
C3[a]	55.2 (t)	55.1 (t)	47.1 (t)	66.1 (t)	58.0 (t)
C (%)[b]	59.25/59.06	66.88/66.51	57.64/57.27	63.14/63.03	74.12/73.74
H (%)[b]	6.22/6.34	5.61/5.76	5.72/5.92	7.42/7.56	6.68/6.83
N (%)[b]	5.76/5.78	4.59/4.76	6.11/6.12	4.91/4.91	3.20/3.53

a: δ_C in ppm (multiplicity). b: Elemental analysis results; calculated/found.

2.4c, *N*-methylaniline for compound **2.4a,d**, or *N*-phenylaniline for compound **2.4b**, or a dialkylamine, such as dibenzylamine for compound **2.4e**. Formaldehyde (for **2.4a-c**), isobutyraldehyde (for **2.4d**), and 3-phenylpropionaldehyde (for **2.4e**) were each utilized as the aldehyde. It is noteworthy that the Bt-containing intermediate need not be purified in order to give satisfactory yields; an 80% yield for compound **2.4e** was obtained from reaction of the unpurified Bt-containing intermediate. This 80% yield for compound **2.4e**

is comparable to the overall yield (~81%) obtained for the other fluorinated-*beta* amino esters **2.4a-d** when the Bt-containing compound was isolated (~90% yield) and then reacted with Reformatsky reagent (~90% yield). As the Bt-containing intermediate does not require purification for successful further transformation, the final products can in theory be obtained in pure form and high yield in one day from commercially available reagents. As previously mentioned, ethyl 3-(benzylamino)-2,2-difluoro-4-methylpentanoate, from Reformatsky reaction with an iminium cation precursor [92MI1235], was synthesized in two steps in only 64% yield, whereas our yield for the same compound was 89% in only one pot.

Additionally, the *N,N*-dibenzyl compound **2.4e** was transformed into the primary amino compound **2.4f** by reductive debenzylation (Figure 2.9). Compound **2.4e** was hydrogenated ($H_{2(g)}$, 45 psi) in ethanol with 5 mol% $Pd(OH)_2$ on carbon by shaking in a Parr hydrogenator for 2 days (d). Analytically pure compound **2.4f** was obtained in 88% yield by simply filtering away the catalyst and removing the volatiles by rotary evaporation under reduced pressure. Thus, *alpha,alpha*-difluorinated primary-*beta*-amino esters can be generated in 70% overall yield from a three-step procedure utilizing dibenzylamine instead of ammonia as the source of nitrogen.

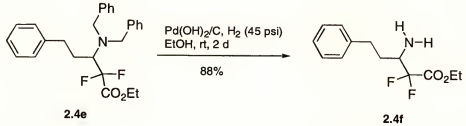


Figure 2.9. Synthesis of a Primary *alpha*, *alpha*-Difluoro-*beta*-Amino Ester

2.2.5 Ethyl *alpha*-Fluoro-*beta*-amino Esters **2.5a-c**

When bromofluoroacetate was used as the Reformatsky reagent precursor in reaction with the iminium cation derived from *N*-(*alpha*-aminoalkyl)benzotriazoles, ethyl *alpha*-fluoro-*beta*-amino esters **2.5a-c** were synthesized in high yields (Figure 2.10, Table 2.2). The method used for the synthesis of the monofluorinated products was the same as that described above for the difluorinated products. Aniline (for compound **2.5a**), *N*-methylaniline (for compound **2.5b**), and dibenzylamine (for compound **2.5c**) were the amine starting reagents and formaldehyde (for compound **2.5a,b**) and 3-phenylpropionaldehyde (for compound **2.5c**) were the aldehydes utilized. Although the

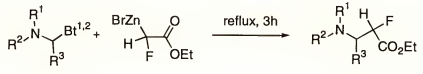


Figure 2.10. Synthesis of *alpha*-Fluoro-*beta*-Amino Esters

Table 2.2. Selected Data for Identification of *alpha*-Fluoro-*beta*-amino Esters **2.5a-c**

Product	**2.5a**	**2.5b**	**2.5c**
R^1	Ph	Ph	CH_2Ph
R^2	Me	H	CH_2Ph
R^3	H	H	$(CH_2)_2Ph$
Yield (%)	91	77	78
mp (°C)	oil	oil	oil
C1[a]	167.9 (d)	168.3 (d)	169.4, 168.8 (d)
C2[a]	88.7 (d)	87.5 (d)	91.5, 87.3 (d)
C3[a]	54.0 (d)	45.6 (d)	58.6, 58.1 (d)
C (%)[b]	63.98/63.65	62.55/62.22	77.30/77.51
H (%)[b]	7.16/7.36	6.68/6.73	7.21/7.34
N (%)[b]	6.22/6.21	6.63/6.76	3.34/3.33

a: δ_C in ppm (multiplicity). b: Elemental analysis results; calculated/found.

yield for compound **2.5b** was low (77% versus 92%) with respect to its difluorinated analog **2.4c**, compounds **2.5a,c** gave yields comparable to those of their difluorinated analogs **2.4a,e**. Compound **2.5c** was obtained as a mixture of diastereoisomers. When the *N,N*-dibenzyl compound **2.5c** was treated with the same debenzylation conditions used for the conversion of compound **2.4e** into the corresponding primary amine, neither starting material nor any products were isolated.

2.2.6 *alpha*-Fluorinated Bis(*beta*-amino Esters) **2.6a-d**

The present method was then further extended to the synthesis of fluorinated bis(*beta*-amino esters) **2.6a-d**. As can be seen from Figure 2.11, Reformatsky reagents (1.5 equiv) generated from either ethyl bromofluoroacetate or ethyl bromodifluoroacetate will replace each and every Bt moiety from a single Bt-containing intermediate, if said compound contains more than one *N*-(*alpha*-aminoalkyl)benzotriazole unit, to give *alpha*-fluorinated bis(*beta*-amino esters) **2.6a-d** in good (79-86%) yields (Table 2.3). Again, the amine could be either a dialkyl amine (as in the piperazino unit of **2.6a,b**) or an aniline derivative (as in compounds **2.6c,d**); the aldehyde used in each case (**2.6a-d**) was formaldehyde.

2.2.7 Properties of *alpha*-Fluorinated *beta*-Amino Esters **2.4a-f, 2.5a-c,** and **2.6a-d**

All of the *beta*-amino esters **2.4a-f, 2.5a-c** and **2.6a-d** gave satisfactory ^{1}H and ^{13}C NMR spectra and microanalysis (C, H, N: ±0.4%). The NMR spectra showed the

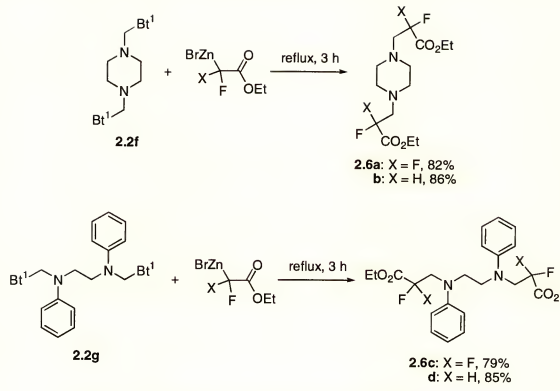


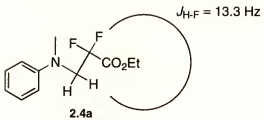
Figure 2.11. Synthesis of *alpha*-Fluorinated Bis(*beta*-amino Esters)

Table 2.3. Selected Data for Identification of *alpha*-Fluorinated Bis(*beta*-amino Esters) **2.6a-d**

Product	**2.6a**	**2.6b**	**2.6c**	**2.6d**
Yield (%)	82	86	79	85
mp (°C)	37-38	83-85	oil	73-75
C1[a]	163.5 (t)	168.7 (d)	163.7 (t)	168.3 (d)
C2[a]	115.8 (t)	88.9 (d)	114.8 (t)	87.9, 87.8 (d)
C3[a]	59.4 (t)	59.2 (d)	54.8 (t)	53.9, 53.8 (d)
C (%)[b]	46.93/46.65	52.16/52.26	59.50/59.50	64.27/64.03
H (%)[b]	6.19/6.38	7.50/7.73	5.83/6.00	6.74/6.97
N (%)[b]	7.82/7.80	8.69/8.66	5.78/5.80	6.25/6.21

a: δ_C in ppm (multiplicity). b: Elemental analysis results; calculated/found.

splitting expected due to coupling with fluorine atoms, when not obscured by other signals, as exemplified for compounds **2.4a** and **2.5a** (Figure 2.12).



C1 = 163.5 ppm (t, J = 31.5 Hz)
C2 = 114.9 ppm (t, J = 254.8 Hz)
C3 = 55.2 ppm (t, J = 16.8 Hz)

C1 = 167.9 ppm (d, J = 23.0 Hz)
C2 = 88.7 ppm (d, J = 186.4 Hz)
C3 = 54.0 ppm (d, J = 21.2 Hz)

Figure 2.12. Represenative Fluorine Couplings

The NMR spectra of ethyl 2,2-difluoro-3-[(phenylmethyl)amino]propanoate (**2.4a**) displayed signals (ppm) corresponding to a monosubstituted benzene ring [δ_H = 7.20-7.14 (m, 2H), 6.76-6.70 (m, 3H); δ_C = 148.7, 128.8, 117.8, 112.8], an *N*-CH_3 group [δ_H = 2.91 (s, 3H; δ_C = 38.8], and a carboxylic ethyl group [δ_H = 4.06 (q, 2H, J = 7.1 Hz), 1.13 (t, 3H, J = 7.1 Hz); δ_C = 62.7, 13.3]. Additional signals, arising from the propanoate unit, showed splitting expected from the C2 fluorine atoms [δ_HC3 = 3.83 (t, 2H, $J_{H\text{-}F}$ = 13.3 Hz); δ_C = 163.5 (t, J = 31.5 Hz, C1), 114.9 (t, J = 254.8 Hz, C2), 55.2 (t, J = 16.8 Hz, C3)]. Selected data for other *alpha*, *alpha*-difluorinated compounds **2.4a-e** are listed in Table 2.1. Compound **2.4b** gave spectra similar to those of compound **2.4a**, except that it showed peaks for an *N,N*-diphenylamino unit [δ_H = 7.12 (t, 4H, J = 7.8 Hz), 6.87 (d, 6H, J = 8.0 Hz); δ_C = 147.6, 129.3, 122.5, 121.4] instead of those for an *N*-methyl-*N*-phenyl unit. Compound **2.4c** gave spectra similar to those of compound **2.4a**, except that it showed peaks for an *N*-phenylamino unit [δ_H = 7.16 (t, 2H, J = 7.4 Hz), 6.75 (t, 1H, J = 7.3 Hz), 6.65 (d, 2H, J = 8.0 Hz), 4.12-3.72 (m, 3H); δ_C = 146.5, 129.2, 118.8, 113.3] instead of for an *N*-methyl-*N*-phenyl unit. Ethyl 3-(dibenzylamino)-2,2-difluoro-5-

phenylpentanoate (**2.4e**) gave much more complex spectra than the other difluorinated analogs. The ^{1}H NMR spectrum did show integration for 15 protons in the aromatic region and 15 protons in the aliphatic region, but the only clear splitting pattern was for the methyl group of the ester [0.96 (t, 3H, J = 7.1 Hz)]. The ^{13}C NMR spectrum clearly showed C-F splitting for C1-C3 consistent with the other analogs **2.4a-d**, as well as 6 other aliphatic carbons, but only 8 aromatic peaks. The product of reductive-debenzylation of compound **2.4e**, ethyl 3-amino-2,2-difluoro-5-phenylpentanoate (**2.4f**), gave much simpler spectra. The ^{1}H NMR spectrum showed a five-proton multiplet [7.27-7.15 (m, 5H)] for the monosubstituted benzene ring, signals for the $CO_2CH_2CH_3$ protons [4.23 (q, 2H, J = 7.1 Hz), 1.24 (t, 3H, J = 7.1 Hz)], and a series of five one-proton multiplets for the pentyl group [3.20-3.17, 2.91-2.83, 2.72-2.62, 1.98-1.86, 1.66-1.54 (m, 3H)], the last signal of which was overlapped with the signal for the NH_2 protons. The ^{13}C NMR spectrum of compound **2.4f** showed peaks for the pentanoate backbone [δ_C = 163.6 (t, J = 32.5 Hz, C1), 115.9 (t, J = 253.4 Hz, C2), 53.4 (t, J = 24.1 Hz, C3), 31.5, 31.2], the aromatic ring (δ_C = 140.9, 128.2, 128.1, 125.8), and the ethyl group (δ_C = 62.4, 13.5).

The NMR spectra for ethyl 2-fluoro-3-(*N*-phenyl-*N*-methylamino)propanoate (**2.5a**) showed the expected signals for the benzene ring [δ_H 7.03 (t, 2H, J = 7.8 Hz), 6.55 (d, 3H, J = 8.3 Hz); δ_C 148.0, 128.7, 116.8, 112.1], the F-C-H unit [δ_H 4.86 (dm, 1H, $^2J_{H\text{-}F}$ = 49.5 Hz); δ_C 88.7 (d, J = 186.4 Hz)], the methylene unit [δ_H 3.73-3.39 (m, 2H); 54.0 (d, J = 21.2 Hz)], the N-CH_3 group [δ_H 2.76 (s, 3H); δ_C 38.6], and the $CO_2CH_2CH_3$ group [δ_H 3.95 (q, 2H, J = 7.1 Hz), 1.04 (t, 3H, J = 7.1 Hz); δ_C 167.9 (d, J =23.0 Hz), 61.1, 13.5]. The spectra for ethyl 2-fluoro-3-(*N*-phenylamino)propanoate (**2.5b**) were quite

similar to those of compound **2.5a**, except the former showed a broad one-proton singlet (^{1}H NMR, δ_H = 4.04 ppm) for the N-H while the latter showed signals for an *N*-CH_3 group [δ_H 2.76 (s, 3H); δ_C 38.6]. The spectra for ethyl 3-(dibenzylamino)-2-fluoro-5-phenylpentanoate (**2.5c**) were even more complicated than those of its difluorinated analog **2.4e** due to it being isolated as a mixture of diastereoisomers. The ^{1}H NMR spectrum was integrated for 15 protons in both the aromatic and aliphatic regions, with no distinct couplings. The ^{13}C NMR spectrum gave a multitude of peaks since most of the carbons of each diastereoisomer gave separate signals. For instance, there were two peaks for C1 [δ_C 169.4 (d, J = 24.2 Hz), 168.8 (d, J = 24.9 Hz)], C2 [δ_C 91.5 (d, J = 189.6), 87.3 (d, J = 191.1 Hz)] and C3 [δ_C 58.6 (d, J = 18.7 Hz), 58.1 (d, J = 18.3 Hz)].

The *alpha*-fluorinated bis(*beta*-amino esters) **2.6a-d** give NMR spectra similar to those of the other esters **2.4a-f**, **2.5a-c**, but unlike them, the bis-esters were usually crystalline (Table 2.3). As expected, the tetrafluorinated bis-ester derived from piperazine **2.6a** gave simple spectra; however, the ethyl groups failed to give clean coupling, possibly due to slight differences in their magnetic environments. Thus, the piperazine fragment gave only one signal [δ_H 2.56 (s, 8H); δ_C 53.6], the methylenes *alpha* to the CF_2 groups [δ_C 115.8 (t, J = 52.7 Hz)] gave a 4-proton multiplet [δ_H 2.97-2.89; δ_C 59.4 (t, J = 26.7 Hz)], and the $CO_2CH_2CH_3$ groups gave appropriate signals [δ_H 4.36-4.29 (m, 4H), 1.36-1.32 (m, 6H); δ_C 163.5 (t, J =31.8 Hz), 62.3, 13.8]. 1,4-Di(2-fluoro-3-ethoxy-3-oxopropyl)piperazine (**2.6b**) gave spectra similar to those of its tetrafluorinated analog **2.6a**, with the expected exceptions. Namely, compound **2.6b** gave proton resonances for the H-C-F protons [δ_H 5.14-5.12 (m, 1H), 4.98-4.95 (m, 1H) ppm] not present in compound **2.6a,** and the carbon signals coupled to the fluorine atoms of compound **2.6b**

appeared as doublets instead of triplets and had smaller coupling constants [168.7 (d, J = 23.6 Hz, *C*=O), 88.9 (d, J = 186.9 Hz, *C*HF), 59.2 (d, J = 19.9 Hz, *C*H_2CHF) than those of analog **2.6a**. The spectra for *N,N'*-diphenyl-*N,N'*-di(2,2-difluoro-3-ethoxy-3-oxopropyl)-1,2-ethylenediamine (**2.6c**) were rather well defined. Besides the signals from the *N,N'*-diphenyl-1,2-ethylenediamine core [δ_H 7.28-7.22 (m, 4H), 6.85-6.79 (m, 6H), 3.61 (s, 4H); δ_C, 147.3, 129.3, 118.8, 114.0, 48.4], the methylene units appeared as a triplet in the ^{1}H NMR spectrum due to coupling with the neighboring fluorine atoms [δ_H 3.91 (t, 4H, J = 13.6 Hz); δ_C 54.8 (t, J = 26.5 Hz)], the $CO_2CH_2CH_3$ groups gave signals with clear coupling in the ^{1}H NMR spectrum [δ_H 4.16 (q, 4H, J = 7.1 Hz), 1.21 (t, 6H, J = 7.1 Hz); δ_C 163.7 (t, J = 31.8 Hz), 63.1, 13.7], and the two CF_2 units appeared as a triplet in the ^{13}C NMR spectrum [δ_C 114.8 (t, J = 254.7 Hz)]. The only distinct coupling in the ^{1}H NMR spectrum of *N,N'*-diphenyl-*N,N'*-di(2-fluoro-3-ethoxy-3-oxopropyl)-1,2-ethylenediamine (**2.6d**) was for the geminal H-F [5.07 (dm, 2H, $^2J_{H\text{-}F}$ = 49.5 Hz)]; the spectrum integrated for 10 aromatic protons and 20 aliphatic protons as expected. As expected in the ^{13}C NMR spectrum for compound **2.6d**, not all of the chemically equivalent carbons gave a single resonance. There were 1 carbonyl signal [δ_C 168.3 (d, J = 23.3 Hz)], 5 aromatic signals [δ_C 146.7, 146.6, 129.5, 117.5, 112.5], 2 signals for the CHF carbons [δ_C 87.9 (d, J = 186.3 Hz), 87.8 (d, J = 186.3 Hz)], and only two signals for the ethyl groups [δ_C 61.7, 14.0], but a distinct signal for each of the CH_2 carbons [δ_C 53.9 (d, J = 21.1 Hz), 53.8 (d, J = 21.2 Hz), 48.9, 48.8].

In conclusion, the Reformatsky reaction of bromofluoroacetates with *N*-(*alpha*-aminoalkyl)benzotriazoles was developed, and its utility in the synthesis of mono- and di-fluorinated *beta*-amino esters **2.4a-f** and **2.5a-c**, respectively, was shown. In addition to

supplementing other methods for such compounds, this approach has led to the first synthesis of *alpha*-fluorinated bis(*beta*-amino esters) **2.6a-d**.

2.3 Experimental

2.3.1 General Comments

All melting points were measured on a hot-stage microscope and are uncorrected. NMR experiments were conducted with a Varian VXR-300 NMR spectrometer at 75 MHz for ^{13}C and 300 MHz for ^{1}H spectra. Samples were dissolved in deuteriochloroform with the internal reference being TMS (δ_H = 0.00 ppm) for ^{1}H spectra and solvent (δ_C = 77.0 ppm) for ^{13}C spectra. Elemental analyses were performed on a Carlo Erba-1106 elemental analyzer. Immediately prior to use, THF and diethyl ether were distilled from sodium/benzophenone; toluene was distilled from sodium. Column chromatography was carried out using 230-400 mesh silica gel. Methylene chloride was dried over 4Å molecular sieves. Molecular sieves were activated by microwave irradiation. All other chemicals were obtained from commercial sources and were not further purified. Reactions were carried out under dry nitrogen or argon with magnetic stirring.

Preparations and characterizations of the *N*-(*alpha*-aminoalkyl)benzotriazoles **2.2a-d,f,g** have been published [75JCS(P1)1181, 87JCS(P1)781, 95JOC3993, 98JOC6712].

1-(*N*-Methyl-*N*-phenylaminomethyl)benzotriazole (**2.2a**) [75JCS(P1)1181]. A mixture of *N*-methylaniline (50 mmol), BtH (50 mmol), and formaldehyde (50 mmol, 37% in water) was refluxed in toluene for 2 h with azeotropic removal of water. After removal of volatiles under vacuum, the condensation product was crystallized from

diethyl ether: hexanes (20:1). The title compound was obtained as a 4.17:1 Bt^1:Bt^2 mixture as white rods, mp 75-77 °C (lit. mp 76-78 °C); ^{1}H NMR (minor isomer in square brackets) δ_H 8.03-8.00 (m, 1H) [7.87-7.84 (m, 2H)], 7.36-7.16 (m, 5H), 7.09-6.88 (m, 3H), [6.16 (s, 2H)] 6.14 (s, 2H), [3.31 (s, 3H)] 3.02 (s, 3H); ^{13}C NMR δ_C 147.8, 146.1, 132.5, 129.4, 129.2, 127.4, 126.4, 123.8, 120.0, 119.8, 119.1, 118.3, 115.2, 113.7, 110.1, 72.7, 66.8, 38.8, 37.5.

1-(*N*,*N*-Diphenylaminomethyl)benzotriazole (**2.2b**) [87JCS(P1)781]. A mixture of *N*-phenylaniline (50 mmol), BtH (50 mmol), and formaldehyde (50 mmol, 37% in water) was refluxed in ethanol for 16 h. After removal of volatiles under vacuum, the condensation product was crystallized from diethyl ether. The title compound was obtained as colorless prisms (diethyl ether), mp 108-109 °C; ^{1}H NMR δ_H 7.97 (d, 1H, J = 7.8 Hz), 7.31-7.17 (m, 10H) 7.06 (t, 2H, J = 6.9 Hz), 6.74 (d, 1H, J = 7.5 Hz), 6.45 (s, 2H); ^{13}C NMR δ_C 146.5, 146.0, 132.8, 129.6, 127.2, 123.8, 123.3, 121.8, 119.6, 110.1, 65.3. Anal. Calcd for $C_{19}H_{16}N_4$: C, 75.98; H, 5.37; N, 18.65. Found: C, 76.03; H, 5.43; N, 18.82.

1-(*N*-Phenylaminomethyl)benzotriazole (**2.2c**) [75JCS(P1)1181]. A mixture of aniline (50 mmol), BtH (50 mmol), and formaldehyde (50 mmol, 37% in water) was stirred in diethyl ether (50 mL) at rt for 2 h. The pure product, which precipitated from the solution, was isolated by vacuum filtration. The title compound was obtained as a 3:1 Bt^1:Bt^2 mixture as white needles (ethanol), mp 138-140 °C (lit. mp 141-143 °C); ^{1}H NMR (minor isomer in square brackets) δ_H 8.04 (d, 1H, J = 8.4 Hz) [7.86 (dd, 2H, J = 6.6, 3.0 Hz)], 7.64 (d, 1H, J = 8.4 Hz), 7.47-7.32 (m, 2H), 7.17 (t, 2H, J = 7.8 Hz), 6.92-6.77 (m, 3H), 6.08 (d, 2H, J = 6.9 Hz), [5.38 (br/t, 1H)] 5.13 (br/t, 1H); ^{13}C NMR δ_C

146.3, 144.9, 132.5, 129.5, 129.4, 127.6, 126.6, 124.2, 120.1, 119.9, 118.3, 113.9, 109.9, 64.8, 58.2.

1-[1-(*N*-Methyl-*N*-phenylamino)-2-methylpropyl]benzotriazole (**2.2d**) [95JOC3993]. A mixture of *N*-methylaniline (50 mmol), isobutyraldehyde (60 mmol), BtH (50 mmol), *p*-toluenesulfonic acid monohydrate (1.25 mmol), 4Å molecular sieves, and diethyl ether was shaken for 1 h. Pure compound was isolated by filtration, removal of volatiles under vacuum, and subsequent crystallization form diethyl ether. The title compound was obtained as a 1.75:1 mixture of Bt^1:Bt^2 isomers and as colorless rods (diethyl ether), mp 67-69 °C (lit. mp 71-74 °C); ^{1}H NMR (minor isomer in square brackets) δ_H 8.02-7.99 (m, 1H), [7.86 (dd, 2H, *J* = 6.6, 3.1 Hz)], [7.34 (dd, 2H, *J* = 6.6, 3.1 Hz)], 7.27-7.02 (m, 5H), 6.92-6.79 (m, 3H), 5.93 (d, 1H, *J* = 10.7 Hz) [6.12 (d, 1H, *J* = 10.5 Hz)], 3.49-3.28 (m, 1H) [3.16-3.00 (m, 1H)], 2.83 (s, 3H) [3.20 (s, 3H)], 1.28 (d, 3H, *J* = 6.8 Hz) [1.16 (d, 3H, *J* = 6.7 Hz)], 0.87 (d, 3H, *J* = 6.3 Hz) [0.72 (d, 3H, *J* = 6.5 Hz)] ^{13}C NMR δ_C 149.9, 145.4, 143.6, 133.6, 129.3, 129.2, 127.1, 126.1, 123.7, 120.0, 119.6, 119.2, 118.3, 116.1, 114.8, 109.9, 86.4, 81.5, 32.2, 31.5, 31.4, 29.9, 19.6, 19.1.

N,N'-Bis(benzotriazol-1-ylmethyl)piperazine (**2.2f**) [87JCS(P1)781]. A mixture of piperazine (25 mmol), BtH (50 mmol), and formaldehyde (50 mmol, 37% in water) was refluxed in toluene for 2 h with azeotropic removal of water. After removal of volatiles under vacuum, the condensation product was crystallized from ethanol. The title compound was obtained as white powder (ethanol), mp 172-175 °C; ^{1}H NMR δ_H 8.09-7.94 (m, 2H), 7.61-7.48 (m, 2H), 7.24-7.02 (m, 4H), 6.00 (s, 4H), 3.73 (s, 8H); ^{13}C NMR δ_C 146.1, 132.6, 129.8, 123.9, 116.7, 109.8, 65.8, 47.6.

N,N'-Bis(benzotriazol-1-ylmethyl)-*N,N'*-diphenylethylenediamine (**2.2g**) [98JOC6712]. A mixture of 1,2-dianilinoethane (25 mmol), BtH (50 mmol), and formaldehyde (50 mmol, 37% in water) was refluxed in toluene for 2 h with azeotropic removal of water. After removal of volatiles under vacuum, the condensation product was crystallized from ethanol. The title compound was obtained as white needles (ethanol), mp 154-155 °C (lit. mp 151-154 °C); ^{1}H NMR δ_H 8.11-7.91 (m, 2H), 7.52-7.14 (m, 9H), 7.13-6.81 (m, 7H), 6.02 (s, 4H), 3.71 (s, 4H); ^{13}C NMR δ_C 146.4, 146.1, 132.6, 129.8, 127.5, 123.9, 121.0, 119.9, 116.7, 109.8, 66.0, 47.3.

1-Dibenzylamino-2-phenylethylene (**2.3**). To a 250 mL round-bottomed flask was added BtH (2.98 g, 25 mmol), dibenzylamine (2.92 mL, 25 mmol), 50 mL of ethanol, and phenylacetaldehyde (4.8 g, 25 mmol). After 12 h of stirring, the title compound was collected by vacuum filtration as a white powder in 85% yield, mp 116-119 °C; ^{1}H NMR δ_H 7.35-6.96 (m, 16H), 5.33 (d, 1H, J = 14.0 Hz), 4.30 (s, 4H); ^{13}C NMR δ_C 139.6, 139.0, 137.9, 128.53, 128.48, 127.5, 127.2, 123.6, 123.4, 98.3, 54.7. Anal. Calcd for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found: C, 88.19; H, 7.42; N, 4.71.

2.3.2 General Procedure for the Synthesis of *alpha*-Fluorinated *beta*-Amino Esters **2.4a-e**, **2.5a-c** and **2.6a-d**

To a schlenk flask was added zinc (10 mmol), THF (25 mL), and chlorotrimethylsilane (4 mmol). After 10 min, the appropriate ethyl bromofluoroacetate (7.5 mmol) was added, followed by compound **2.1** (5 mmol) after an additional 10 min. After 3 h of refluxing, the solution was allowed to cool to rt before being quenched with 10 mL of saturated, aqueous $NaHCO_3$ and filtered through Celite 545®. The layers were

separated, and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organics were washed with 10 mL of brine and dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, compounds **2.4-2.6** were isolated in pure form by flash column chromatography (10:1 hexanes:ethyl acetate) of the crude product.

Ethyl 2,2-difluoro-3-[(phenylmethyl)amino]propanoate (**2.4a**). The title compound was obtained as a brown oil; ^{1}H NMR δ_H 7.20-7.14 (m, 2H), 6.76-6.70 (m, 3H), 4.06 (q, 2H, J = 7.1 Hz), 3.83 (t, 2H, J = 13.3 Hz), 2.91 (s, 3H), 1.13 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ_C 163.5 (t, J = 31.5 Hz), 148.7, 128.8, 117.8, 114.9 (t, J = 254.8 Hz), 112.8, 62.7, 55.2 (t, J = 16.8 Hz), 38.8, 13.3. Anal. Calcd for $C_{12}H_{15}F_2NO_2$: C, 59.25; H, 6.22; N, 5.76. Found: C, 59.06; H, 6.34; N, 5.78.

Ethyl 2,2-difluoro-3-(diphenylamino)propanoate (**2.4b**). The title compound was obtained as a yellow oil; ^{1}H NMR δ_H 7.12 (t, 4H, J = 7.8 Hz), 6.87 (d, 6H, J = 8.0 Hz), 4.24 (t, 2H, J = 12.9 Hz), 3.87 (q, 2H, J = 7.1 Hz), 0.99 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ_C 163.5 (t, J =31.4 Hz), 147.6, 129.3, 122.5, 121.4, 114.2 (t, J = 253.5 Hz), 62.9, 55.1 (t, J = 27.6 Hz), 13.5. Anal. Calcd for $C_{17}H_{17}F_2NO_2$: C, 66.88; H, 5.61; N, 4.59. Found: C, 66.51; H, 5.76; N, 4.76.

Ethyl 2,2-difluoro-3-(phenylamino)propanoate (**2.4c**). The title compound was obtained as a colorless oil; ^{1}H NMR δ_H 7.16 (t, 2H, J = 7.4 Hz), 6.75 (t, 1H, J = 7.3 Hz), 6.65 (d, 2H, J = 8.0 Hz), 4.22 (q, 2H, J = 7.0 Hz), 4.12-3.72 (m, 3H), 1.25 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ_C 163.5 (t, J =32.1 Hz), 146.5, 129.2, 118.8, 114.4 (t, J = 253.2 Hz), 113.3, 63.0, 47.1 (t, J = 27.8 Hz), 13.7. Anal. Calcd for $C_{11}H_{13}F_2NO_2$: C, 57.64; H, 5.72; N, 6.11. Found: C, 57.27; H, 5.92; N, 6.12.

Ethyl 2-fluoro-3-(*N*-phenylamino)propanoate (**2.4d**). The title compound was made previously, but no characterization was reported [92MI1235]. White solid (ethyl acetate), mp 52-54 °C; ^{1}H NMR δ_H 7.19 (t, 2H, J = 7.5 Hz), 6.79 (d, 2H, J = 8.3 Hz), 6.72 (t, 1H, J = 7.2 Hz), 4.14-3.98 (m, 2H), 3.84-3.78 (m, 1H), 2.77 (s, 3H), 2.41-2.33 (m, 1H), 1.14 (t, 3H, J = 5.3 Hz), 0.99 (t, 3H, J = 7.1 Hz), 0.80 (d, 3H, J = 6.6 Hz); ^{13}C NMR δ_C 163.8 (t, J = 32.3 Hz), 149.7, 128.9, 117.6, 117.5 (t, J = 247.5 Hz), 113.1, 66.1 (t, J = 24.8 Hz), 62.3, 31.6, 31.5, 26.7, 20.5, 19.5, 19.4, 13.4. Anal. Calcd for $C_{15}H_{21}F_2NO_2$: C, 63.14; H, 7.42; N, 4.91. Found: C, 63.03; H, 7.56; N, 4.91.

Ethyl 3-(dibenzylamino)-2,2-difluoro-5-phenylpentanoate (**2.4e**). The title compound was obtained as a colorless oil; ^{1}H NMR δ_H 7.12-6.92 (m, 15H), 4.06-4.00 (m, 1H), 3.78-3.68 (m, 3H), 3.39-3.21 (m,3H), 2.65-2.52 (m, 2H), 1.92-1.82 (m, 2H), 0.96 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ_C 163.9 (t, J = 32.1 Hz), 141.3, 138.8, 129.2, 128.44, 128.48, 128.1, 127.0, 125.9, 118.4 (t, J =257.8 Hz), 62.3, 58.0 (t, J = 21.9 Hz), 54.3, 33.08, 33.04, 25.3, 13.5. Anal. Calcd for $C_{27}H_{29}F_2NO_2$: C, 74.12; H, 6.68; N, 3.20. Found: C, 73.74; H, 6.83; N, 3.53.

Ethyl 3-amino-2,2-difluoro-5-phenylpentanoate (**2.4f**). To a 250 mL hydrogenator bottle was added compound **2.4e** (437 mg, 1 mmol), 50 mL of ethanol, and 4% Pd on carbon (54.7 weight% H_2O, Degussa, 0.15 g). The reactor was attached to a Parr hydrogenator apparatus and the atmosphere was replaced with hydrogen by three successive purges. After 48 h with the pressure of $H_{2(g)}$ maintained at 45 psi, the solution was filtered and concentrated to give the title compound in 88% yield as a white solid (ethyl acetate), decomposes 122 °C; ^{1}H NMR δ_H 7.27-7.15 (m, 5H), 4.23 (q, 2H, J = 7.1 Hz), 3.20-3.17 (m, 1H), 2.91-2.83 (m, 1H), 2.72-2.62 (m, 1H), 1.98-1.86 (m, 1H), 1.66-

1.54 (m, 3H), 1.24 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ_C 163.6 (t, J = 32.5 Hz), 140.9, 128.2, 128.1, 125.8, 115.9 (t, J = 253.4 Hz), 62.4, 53.4 (t, J = 24.1 Hz), 31.5, 31.2, 13.5. Anal. Calcd for $C_{13}H_{17}F_2NO_2$: C, 60.69; H, 6.66; N, 5.44. Found: C, 60.93; H, 6.30; N, 5.28.

Ethyl 2-fluoro-3-(*N*-phenyl-*N*-methylamino)propanoate (**2.5a**). The title compound was obtained as a yellow oil; ^{1}H NMR δ_H 7.03 (t, 2H, J = 7.8 Hz), 6.55 (d, 3H, J = 8.3 Hz), 4.86 (dm, 1H, $^2J_{H\text{-}F}$ = 49.5 Hz), 3.95 (q, 2H, J = 7.1 Hz), 3.73-3.39 (m, 2H), 2.76 (s, 3H), 1.04 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ_C 167.9 (d, J =23.0 Hz), 148.0, 128.7, 116.8, 112.1, 88.7 (d, J = 186.4 Hz), 61.1, 54.0 (d, J = 21.2 Hz), 38.6, 13.5. Anal. Calcd for $C_{12}H_{16}FNO_2$: C, 63.98; H, 7.16; N, 6.22. Found: C, 63.65; H, 7.36; N, 6.21.

Ethyl 2-fluoro-3-(*N*-phenylamino)propanoate (**2.5b**). The title compound was obtained as a yellow oil; ^{1}H NMR δ_H 7.18 (t, 2H, J = 7.7 Hz), 6.75 (t, 1H, J = 7.1 Hz), 6.65 (d, 2H, J = 8.0 Hz), 5.07 (dm, 1H, $^2J_{H\text{-}F}$ = 48.8 Hz), 4.23 (q, 2H, J = 7.0 Hz), 4.04 (br/s, 1H), 3.74-3.52 (m, 2H), 1.27 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ_C 168.3 (d, J = 23.2 Hz), 146.8, 129.2, 118.3, 113.3, 87.5 (d, J = 185.6 Hz), 61.7, 45.6 (d, J = 21.5 Hz), 14.0. Anal. Calcd for $C_{11}H_{14}FNO_2$: C, 62.55; H, 6.68; N, 6.63. Found: C, 62.22; H, 6.73; N, 6.76.

Ethyl 3-(dibenzylamino)-2-fluoro-5-phenylpentanoate (**2.5c**). The title compound was obtained as a colorless oil; ^{1}H NMR δ_H 7.37-7.06 (m, 14H), 6.82 (d, 1H, J = 6.4 Hz), 5.45-4.97 (m, 1H), 4.30-4.24 (m, 0.5H) 4.06-3.82 (m, 3.5H), 3.46-3.35 (m, 2H), 3.18-3.05 (m, 1H), 2.85-2.69 (m, 1H), 2.60-2.57 (m, 1H), 2.43-2.39 (m, 1H), 2.12-2.02 (m, 1.5H), 1.66-1.59 (m, 0.5H), 1.13-1.09 (m, 3H) mixture of diastereoisomers; ^{13}C NMR δ_C 169.4 (d, J = 24.2 Hz), 168.8 (d, J = 24.9 Hz), 141.8, 141.3, 139.5, 139.3, 129.2, 129.1, 128.5, 128.4, 128.3, 128.2, 128.0, 127.1, 126.9, 126.1, 125.6, 91.5 (d, J = 189.6), 87.3 (d,

J = 191.1 Hz), 61.4, 61.2, 58.6 (d, J = 18.7 Hz), 58.1 (d, J = 18.3 Hz), 55.1, 55.0, 54.3, 33.0, 32.2, 27.84, 27.77, 25.4, 13.8. Anal. Calcd for $C_{27}H_{30}FNO_2$: C, 77.30; H, 7.21; N, 3.34. Found: C, 77.51; H, 7.34; N, 3.33.

Ethyl 3-[4-(ethoxy-2,2-difluoro-3-oxopropyl)piperazino]-2,2-difluoropropanoate (**2.6a**). The title compound was obtained as yellow needles (ethyl acetate), mp 37-38 °C; ^{1}H NMR δ_H 4.36-4.29 (m, 4H), 2.97-2.89 (m, 4H), 2.56 (s, 8H), 1.36-1.32 (m, 6H); ^{13}C NMR δ_C 163.5 (t, J =31.8 Hz), 115.8 (t, J = 52.7 Hz), 62.3, 59.4 (t, J = 26.7 Hz), 53.6, 13.8. Anal. Calcd for $C_{14}H_{22}F_4N_2O_4$: C, 46.93; H, 6.19; N, 7.82. Found: C, 46.65; H, 6.38; N, 7.80.

1,4-Di(2-fluoro-3-ethoxy-3-oxopropyl)piperazine (**2.6b**). The title compound was obtained as colorless rods (ethyl acetate), mp 83-85 °C; ^{1}H NMR δ_H 5.14-5.12 (m, 1H), 4.98-4.95 (m, 1H), 4.31-4.23 (m, 4H), 2.93-2.81 (m, 4H), 2.64-2.53 (m, 8H), 1.31 (t, 6H, J = 7.0 Hz); ^{13}C NMR δ_C 168.7 (d, J = 23.6 Hz), 88.9 (d, J = 186.9 Hz), 61.4, 59.2 (d, J = 19.9 Hz), 53.6, 14.2. Anal. Calcd for $C_{14}H_{24}F_2N_2O_4$: C, 52.16; H, 7.50; N, 8.69. Found: C, 52.26; H, 7.73; N, 8.66.

N,N'-Diphenyl-*N,N'*-di(2,2-difluoro-3-ethoxy-3-oxopropyl)-1,2-ethylenediamine (**2.6c**). The title compound was obtained as a yellow oil; ^{1}H NMR δ_H 7.28-7.22 (m, 4H), 6.85-6.79 (m, 6H), 4.16 (q, 4H, J = 7.1 Hz), 3.91 (t, 4H, J = 13.6 Hz), 3.61 (s, 4H), 1.21 (t, 6H, J = 7.1 Hz); ^{13}C NMR δ_C 163.7 (t, J = 31.8 Hz), 147.3, 129.3, 118.8, 114.8 (t, J = 254.7 Hz), 114.0, 63.1, 54.8 (t, J = 26.5 Hz), 48.4, 13.7. Anal. Calcd for $C_{24}H_{28}F_4N_2O_4$: C, 59.50; H, 5.83; N, 5.78. Found: C, 59.50; H, 6.00; N, 5.80.

N,N'-Diphenyl-*N,N'*-di(2-fluoro-3-ethoxy-3-oxopropyl)-1,2-ethylenediamine (**2.6d**). The title compound was obtained as white prisms (ethyl acetate), mp 73-75 °C; ^{1}H

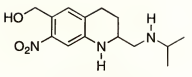
NMR δ_H 7.28-7.23 (m, 4H), 6.80-6.77 (m, 6H), 5.07 (dm, 2H, $^2J_{H\text{-}F}$ = 49.5 Hz), 4.24-4.22 (m, 4H), 4.02-3.84 (m, 2H), 3.76-3.57 (m, 6H), 1.30-1.20 (m, 6H); ^{13}C NMR δ_C 168.3 (d, J = 23.3 Hz), 146.7, 146.6, 129.5, 117.5, 112.5, 87.9 (d, J = 186.3 Hz), 87.8 (d, J = 186.3 Hz), 61.7, 53.9 (d, J = 21.1 Hz), 53.8 (d, J = 21.2 Hz), 48.9, 48.8, 14.0. Anal. Calcd for $C_{24}H_{30}F_2N_2O_4$: C, 64.27; H, 6.74; N, 6.25. Found: C, 64.03; H, 6.97; N, 6.21.

CHAPTER 3
SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOLINES *VIA N*-(*ALPHA*-AMINOALKYL)BENZOTRIAZOLES

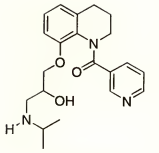
3.1 Introduction

As recently reviewed [96T15031], 1,2,3,4-tetrahydroquinolines play a multitude of roles in medicinal and industrial chemistry because of their significant biological activity and interesting properties. Although some 1,2,3,4-tetrahydroquinolines of biological interest are naturally occurring, most are synthetic. More specifically, 2-methyl-1,2,3,4-tetrahydroquinoline has been isolated from the human brain, and some complex molecules built on the 1,2,3,4-tetrahydroquinoline system, such as Dynemycin, are natural antitumor antibiotics, bradykinin antagonists, or interact with *alpha*-adrenergic, histaminergic, and muscarinic receptors.

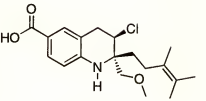
Among the plethora of potential drugs obtained synthetically and having the 1,2,3,4-tetrahydroquinoline substructure, several are currently commercially available. For instance (Figure 3.1), oxamniquine (**3.1**) is a schistosomicide, nicainoprol (**3.2**) is an antiarrhythmic drug, viratmycin (**3.3**) is an antibiotic, and 1,2,3,4-tetrahydroquinoline-4-carboxylic acid is a component in some tissue irrigating solutions. Although not marketed, many more 1,2,3,4-tetrahydroquinolines have been shown to exhibit analgesic properties and behave as inhibitors or antagonists toward a number of enzymes, systems, or disorders of human beings.



3.1 oxamniquine



3.2 nicainoprol



3.3 viratmycin

Figure 3.1. Pharmaceuticals Having a 1,2,3,4-Tetrahydroquinoline Nucleus

In the non-pharmaceutical industry, 1,2,3,4-tetrahydroquinolines have found wide spread applications in agrochemistry, fuel chemistry, dye chemistry, and photography. More specifically, the 1,2,3,4-tetrahydroquinoline-based dyes are used for dyeing hair, acrylic fibers, polyesters, and polyamides, while in the photographic industry 1,2,3,4-tetrahydroquinolines are used as intermediates for photographic couplers as well as for high sensitivity photosensitizers and charge transporting agents.

Many methods have been reported for the synthesis of 1,2,3,4-tetrahydroquinolines **3.4** (Figure 3.2) [96T15031]. A few of the synthetic routes to 1,2,3,4-tetrahydroquinolines involve direct reductions of quinolines **3.5** [96T1631] and 1,2-dihydroquinolines **3.6** [89S221, 90CPB2577, 92JOC4404], derivatization of other 1,2,3,4-tetrahydroquinolines [86T5407, 90JOC1744, 92SL143, 93JOC6538], and ring

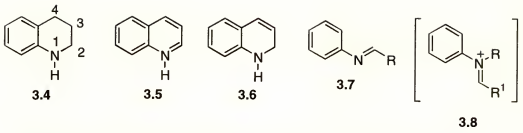


Figure 3.2. Reagents for the Synthesis of 1,2,3,4-Tetrahydroquinolines

closure of imines **3.7** [96T15031, 94CHE64, 95CL423, 95S801, 95TL5943, 96SL669, 92SC2433, 93JOC4509, 87MI278, 74MI305]. Among the currently available methods to 1,2,3,4-tetrahydroquinolines, cycloaddition reactions of *N*-arylalkyleneiminium cations **3.8** with olefins [69JCS(CC)20, 70LA117, 82JA5753, 91TL7103, 95T6115, 92SL835, 95JCS(CC)2137, 96SL34, 93JOC4049, 94JOC607, 95JOC7631, 95S1195, 96TL7357, 96JA8977] are highly attractive, but existing application of these methods all display some limitations. First of all, some of the starting materials are difficult to obtain and/or manipulate [96SL669, 82JA5753, 95JCS(CC)2137, 94JOC607]; such is the case of *ortho*-aminoalkyl alcohols **3.9**, which are precursors of the highly reactive *ortho*-quinone methide imine intermediate **3.10** in a Diels-Alder reaction with alkenes (Figure 3.3) [96SL669]. Second, sometimes only activated alkenes can be utilized in the cycloaddition reaction [95CL423, 91TL7103, 93JOC4049, 94JOC607, 95S1195, 96TL7357, 96JA8977]; for example Mellor's procedure only used styrenes and enol ethers as the alkene reagent [91TL7103]. Lastly, 2-substituted- and *N*-unsubstituted-1,2,3,4-tetrahydroquinolines are difficult to prepare [82JA5753, 92SL835, 95JCS(CC)2137, 96SL34].

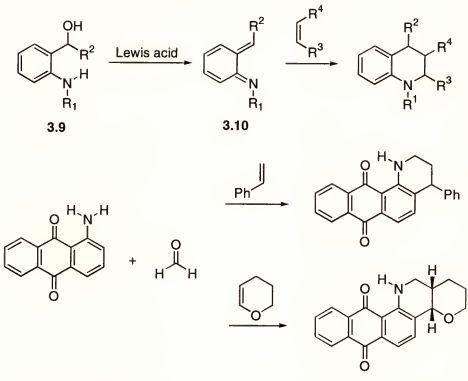
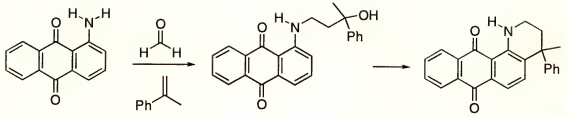


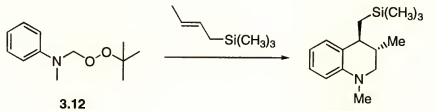
Figure 3.3. Formation of 1,2,3,4-Tetrahydroquinolines by Cycloadditions

The mechanism of the reaction of *N*-arylalkyleneiminium cations with olefins remains uncertain. Early work of Swan [69JCS(CC)20] proposed a polar 1,4-cycloaddition for electron-rich alkenes; however, Shono *et al.* [82JA5753] rationalized their results as a two-step process. In support of the latter mechanism, Mellor and co-workers [91TL7103, 95T6115] isolated a reaction intermediate **3.11**, which was then cyclized to give the 1,2,3,4-tetrahydroquinoline (Figure 3.4). Observed high degrees of retention of the stereochemistry of the olefins in the product, which is usually interpreted as evidence for a concerted cyclization reaction mechanism, were interpreted by the authors [76AGE9] as analogous to high stereoselectivities observed in related multistep cyclizations. Additionally (Figure 3.5), Murahashi *et al.* [92SL835] found that *trans*-1,3-dimethyl-4-(trimethylsilylmethyl)-1,2,3,4-tetrahydroquinoline (**3.13**) was obtained

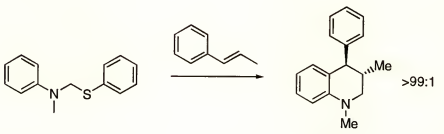


3.11

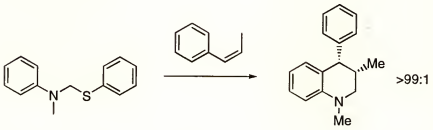
Figure 3.4. Isolation of the Intermediate in a Cycloaddition



3.12 **3.13**



3.14



3.15

Figure 3.5. Conservation of Stereochemistry in Cycloadditions

stereoselectively (trans/cis = 94/6) by the $TiCl_4$-induced reaction of *N*-(*t*-butyldioxymethyl)-*N*-methylaniline (**3.12**) with crotyltrimethylsilane (E/Z = 4/1). More recently, Beifuss and co-workers [95JCS(CC)2137, 96SL34] again observed high stereospecificity for these reactions: the stereochemistries of the dienophiles (E or Z) were preserved almost completely, even though AM1 and PM3 calculations showed that the trans-tetrahydroquinoline **3.14** was more stable than the cis-isomer **3.15**. Together with the fact that no side products could be isolated, these workers [95JCS(CC)2137, 96SL34] interpreted their results in terms of a one-step concerted polar cycloaddition.

N-(*alpha*-Aminoalkyl)benzotriazoles **3.16a,b,** readily synthesized and crystalline solids [91T2683, 94AA31, 94CSR363, 94S445], are known to exist in equilibrium with the corresponding *N*-arylalkyleneiminium cations and Bt anion in solution (Figure 3.6) [95IJCK351]. *N*-(*alpha*-Aminoalkyl)benzotriazoles have been shown by previous work

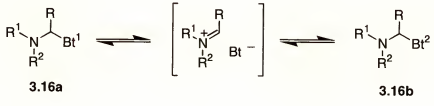


Figure 3.6. Solution Phase Equilibrium of *N*-(*alpha*-Aminoalkyl)benzotriazoles

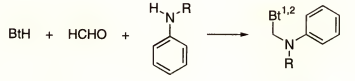
in our group to form 1,4-, 1,3- and 1,3,4-substituted-1,2,3,4-tetrahydroquinolines in moderate yield by acid-catalyzed cyclization with an activated olefin such as a vinyl ether [95JOC2588] or an enamine [95JOC3993]. In order to extend this methodology and improve upon similar reactions of methyleneiminium cations with olefins, the current

investigation was undertaken. The goals were to successfully react *N*-(*alpha*-aminoalkyl)benzotriazoles **3.16a,b** with unactivated alkenes, to synthesize 2-substituted and *N*-unsubstituted 1,2,3,4-tetrahydroquinolines and to provide more evidence toward uncovering the reaction mechanism for formation of 1,2,3,4-tetrahydroquinolines from *N*-arylalkyleneiminium cations and olefins.

3.2 Results and Discussion

3.2.1 *N*-(*alpha*-Aminoalkyl)benzotriazoles **3.17a-c** and **3.18a-c**

Initially, the intermediates containing Bt used toward the synthesis of the 1,2,3,4-tetrahydroquinolines were *N*-(*alpha*-aminoalkyl)benzotriazoles **3.17a-c** (Figure 3.7). This type of compound has been synthesized by aminomethylation (Mannich reaction) of BtH with aldehydes and either arylamines or dialkylamines [87JCS(P1)799]. Syntheses of the *N*-(*alpha*-aminoalkyl)benzotriazoles, **3.17a** [75JCS(P1)1181], **b** [87JCS(P1)799] and **c** [89OPPI135] were discussed in detail in Chapter 2 and therefore will not be expounded upon here.

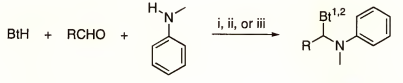


3.17

3.17a: R = Me
b: R = Ph
c: R = H

Figure 3.7. Previously Discussed *N*-(*alpha*-Aminoalkyl)benzotriazoles

However, *N*-(*alpha*-aminoalkyl)benzotriazoles **3.18a-c**, which were to be used in later reactions, will be described here (Figure 3.8). All attempts at synthesizing compound **3.18a**, which were performed using equimolar amounts of acetaldehyde, BtH, and *N*-methylaniline, failed to produce the desired product. Methods utilized included refluxing in toluene with a Dean-Stark trap, shaking in diethyl ether with 4Å molecular sieves, and refluxing in ethanol. Benzotriazole-containing intermediates **3.18b** [90T8153] and **3.18c** [95JOC3993] were each synthesized by shaking an equimolar mixture of either butyraldehyde or benzaldehyde with BtH, *N*-methylaniline, diethyl ether, and 4Å molecular sieves for 2 h; removal of volatiles afforded analytically pure product (Figure 3.8) in yield comparable to that obtained in the literature. Spectroscopic data for compounds **3.18b,c** matched the literature data. Although compound **3.18b** was previously reported to be an oil, the mp determined for compound **3.18c** (123-126 °C) was comparable with the literature value (121-125 °C). As with other *N*-(*alpha*-aminoalkyl)benzotriazoles, these were each isolated as a mixture of Bt^1 and Bt^2 isomers (see Chapter 2 for details on how the isomers were distinguishing from one another).



3.18

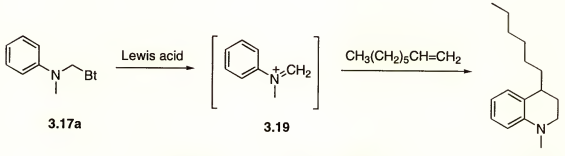
i) Et_2O, 4A MS, rt, 2 h
ii) toluene, Dean-Stark, reflux, 6 h
iii) ethanol, reflux, 16 h

3.18	R	Method	Yield(%)
a	Me	i, ii, iii	0
b	Pr	i	89
c	Ph	i	86

Figure 3.8. Synthesis of Other *N*-(*alpha*-Aminoalkyl)benzotriazoles

3.2.2 Effect of Selected Lewis Acids on the Reaction of Compound **3.17a** With 1-Octene

It has been reported [95IJCK351] that *alpha*-aminomethylenebenzotriazoles **3.16a,b** exist in equilibrium with the iminium cation **3.6** and Bt anion in solution (Figure 3.6). Taking advantage of such ionization property, we reacted *alpha*-aminomethylenebenzotriazole **3.17a** with 1-octene in the presence of boron trifluoride etherate (BF_3•Et_2O, 2 equiv) to give tetrahydroquinoline **3.20a** in 85% isolated yield (Figure 3.9). Interestingly, in a Markovnikov fashion, the alkene carbon with the electron-donating group regiospecifically became C4 of the formed 1,2,3,4-tetrahydroquinoline. Among other Lewis acids used for the same reaction, tin (IV) chloride (0.5-2 equiv) and titanium (IV) chloride (2 equiv) assisted in giving compound **3.20a** in 98% and 79% yields, respectively, according to GC analysis. The use of zinc bromide (2 equiv) resulted only in conversion of the starting Bt-containing compound into *N*-methylaniline and *N,N*-dimethylaniline, and no reaction occurred using ytterbium



Lewis acid	Yield (%) of **3.20a**
$Yb(OSO_2CF_3)_3$	0
$ZnBr_2$	0
$TiCl_4$	79
BF_3·EtO_2	85
$SnCl_4$	98

Figure 3.9. Effects of Lewis Acids on Product Yield

triflate monohydrate [$Yb(OSO_2CF_3)_3 \bullet H_2O$, 10 mol%]. Thus, it appears that ytterbium triflate inhibits ionization of the starting Bt-containing reactant. In contrast, zinc bromide appears to assist in the cleavage of either of the two C-N bonds (PhN-C or Bt-C), thereby resulting in formation of *N*-methylaniline and *N,N*-dimethylaniline. Our results show that while zinc bromide may shift the equilibrium to the iminium cation and Bt anion, $BF_3 \bullet Et_2O$, $SnCl_4$, and $TiCl_4$ also assist the iminium cation **3.19** in reaction with 1-octene to afford 1,2,3,4-tetrahydroquinoline **3.20a**. The oil **3.20a** was characterized by comparison of its NMR spectra with those previously published [82JA5753].

3.2.3 Reaction of Compound **3.17a** With Unactivated Alkenes

After testing the affects of various Lewis acids on the reaction of the iminium ion precursor **3.17a** with 1-octene, the reaction of two other unactivated alkenes, 1-hexene and 1-octene, with compound **3.17a** were tested (Figure 3.10, Table 3.1). The method consisted of treating a solution of intermediate **3.17a** (2 mmol) and alkene (4 mmol) in dry methylene chloride (10 mL) at 0 °C with Lewis acid (4 mmol) dissolved in dry methylene chloride (10 mL) under an atmosphere of argon. After being stirred for 2 h, the reaction was quenched with water (8mL). After work-up, as described in the experimental section, the crude product was subjected to GC/MS analysis and then the components were separated by column chromatography to give the pure 4-alkyl-1-methyl-1,2,3,4-tetrahydroquinolines **3.20a-c**. The columns were eluted with a rather nonpolar solvent system, typically 200:1 hexanes:ethyl acetate. Initially, isolated yields were quite poor (<15%), but the use of 0.5% triethylamine in the eluent increased the yields substantially. Also, isolated yields were higher when the separation was performed

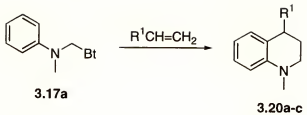


Figure 3.10. Reaction of 1-(*N*-Methyl-*N*-phenylaminomethyl)benzotriazole With Unactivated Alkenes

Table 3.1. Synthesis of 1,2,3,4-Tetrahydroquinolines **3.20a-c** From 1-(*N*-Methyl-*N*-phenylaminomethyl)benzotriazole (**3.17a**) and Unactivated Alkenes

Compound **3.20**	R^1	Lewis acid	GC yield (%)	Isolated yield (%)
a	n-C_6H_{13}	$SnCl_4$	98	85
b	n-C_4H_9	BF_3Et_2O	84	62
c	n-C_8H_{17}	BF_3Et_2O	87	56

by flash column chromatography (<1 h, 56% yield for **3.20c**) rather than by gravity column chromatography (>6 h, 33% yield for **3.20c**). This information, when added to the fact that GC yields were substantially higher than even the best isolated yield after flash column chromatography with the use of triethylamine, suggests that the 1,2,3,4-tetrahydroquinoline products slowly decompose during silica gel column chromatography. The use of alumina gel instead of silica gel with triethylamine did not substantially improve yields. The oily products **3.20b** [95JOC2588] and **3.20c** [95JOC7631] were characterized by comparison of their NMR spectra with those in the literature.

3.2.4 Retention of Olefin Stereochemistry

After the initial success of reacting iminium ion precursor **3.17a** with unactivated alkenes, the mechanism of this cyclization was probed by seeing if the stereochemistries of the alkenes would be maintained in the products. As mentioned earlier, cyclizations with 1-alkenes occurred in a Markovnikov fashion; this pattern continued when styrenes were used as the olefin (Figure 3.11, Table 3.2). Thus, the boron trifluoride-induced reaction of compound **3.17a** with styrene gave 1-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline (**3.20d**) with *N*-methylaniline as the only by-product. Reaction of *trans-beta*-methylstyrene in the presence of $SnCl_4$ gave a nearly quantitative yield of

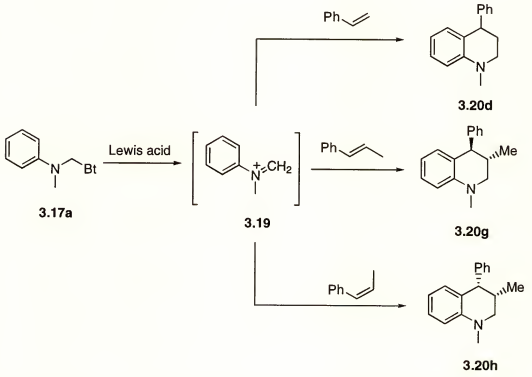


Figure 3.11. Reaction of 1-(*N*-Methyl-*N*-phenylaminomethyl)benzotriazole With Styrenes

Table 3.2. Synthesis of 1,2,3,4-Tetrahydroquinolines **3.20d-h** From *N*-(*alpha*-Aminoalkyl)benzotriazoles **3.17a,b** With Alkenes

Product **3.20**	R	R^1	R^2	Lewis acid	Yield (%) [a]
d	Me	Ph	H	BF_3•Et_2O	78 (95)
e [b]	Me	-$(CH_2)_3$-		BF_3•Et_2O	55 (94)
f [b]	Ph	-$(CH_2)_3$-		$SnCl_4$	63 (97)
g [c]	Me	Ph	CH_3	$SnCl_4$	84 (98)
h [d]	Me	Ph	CH_3	$SnCl_4$	66 (86)

a: Gas chromatograph yields in parentheses. b: Only the cis-isomer was obtained from the cis-alkene. c: Only the trans-isomer was obtained from the trans-alkene. d: A cis/trans = 95/5 mixture of *beta*-methylstyrene was used, and the crude product had a cis/trans = 95/5 ratio as well.

desired product **3.20g**. Similarly, a *cis-beta*-methylstyrene (19:1 ratio with the trans-isomer) gave a high yield of a 19:1 cis-trans mixture of the expected crude product **3.20h**; therefore, the stereochemistry of the alkene was retained in the product. Lastly, the cyclic alkene cyclopentene was utilized as the olefin in reaction with compounds **3.17a,b** to give high yields of only the corresponding cis addition products **3.20e,f** (Figure 3.12, Table 3.2). These observations support a concerted, cationic [4+2] cycloaddition in this reaction system.

Structures of 1,2,3,4-tetrahydroquinolines **3.20d** [82JA5753] and **3.20e,g,h** [95JCS(CC)2137] were determined by comparison of their NMR spectra with those previously reported in the literature; mp for the crystalline products **3.20g** (85-86 °C) and **3.20h** (77-78 °C) were not previously reported. 1-Phenyl-3,4-*cis*-propano-1,2,3,4-tetrahydroquinoline (**3.20f**) was isolated as a colorless oil, and gave satisfactory elemental analysis (C, H, N ± 0.4%). Its ^{1}H NMR spectra was quite similar to that of the

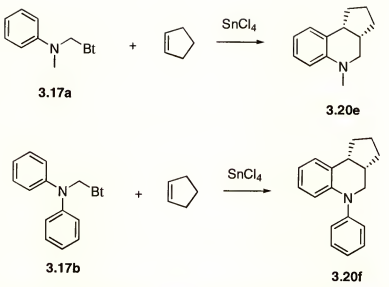


Figure 3.12. Reaction of *N*-(*alpha*-Aminoalkyl)benzotriazoles With Cyclopentene

N-methyl derivative **3.20e**, with the expected differences. Namely, compound **3.20f** gave signals in the aromatic region consistent with an *N*-substituted phenyl ring [δ_H (ppm): 7.27-7.32 (m, 2H), 7.18-7.16 (m, 3H)] instead of the *N*-CH_3 signal of compound **3.20e** [δ_H = 2.83 ppm (s, 3H)]. Correspondingly, the ^{13}C spectra showed four additional aromatic signals, consistent with an *N*-monosubstituted benzene, without the N-CH_3 signal at δ_C = 54.2 ppm.

3.2.5 Synthesis of *N*-Unsubstituted 1,2,3,4-Tetrahydroquinolines

The reaction of intermediate **3.17c** and cyclopentene in the presence of $SnCl_4$ resulted in *N*-unsubstituted 1,2,3,4-tetrahydroquinoline **3.20i** in 20% isolated yield (39% by GC, Figure 3.13). Analysis of the crude product by GC/MS showed that the only other product was *N*-methylaniline, which results from the desired cleavage of the C-Bt bond

without cyclization. Extended reaction time, 24 h instead of 2 h, did not significantly alter the product distribution. This indicates that the lack of a second alkyl group on the nitrogen of the methyleneiminium cation greatly reduces the reactivity of such cations toward reaction with an olefin. This is further evidenced by the fact that reaction of **3.17c** with the less activated alkene 1-octene resulted in quantitative conversion into the *N*-methylaniline by-product.

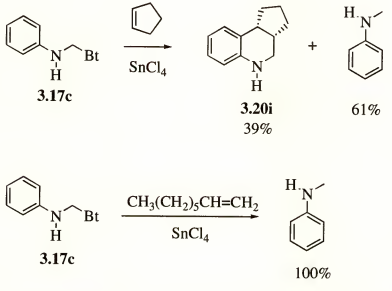


Figure 3.13. Synthesis of an *N*-Unsubstituted 1,2,3,4-Tetrahydroquinoline

3,4-*cis*-Propano-1,2,3,4-tetrahydroquinoline (**3.20i**) was crystallized from hexanes as white needles melting at 43-45 °C, and gave satisfactory elemental analysis (C, H, N ± 0.3%). Its ^{1}H NMR spectra was almost identical to that of the *N*-methyl derivative **3.20e**, however it contained a very broad peak from the N-*H* proton centered around δ_H = 3.82 ppm (1H) instead of the sharp N-*CH*$_3$ singlet at δ_H = 2.83 ppm (3H).

3.2.6 Synthesis of 2-Alkyl-1,2,3,4-tetrahydroquinolines

The last objective of this investigation was to synthesize 2-substituted-1,2,3,4-tetrahydroquinolines. Initial efforts were made using the benzaldehyde-derived intermediate **3.19c** (Figure 3.14). However, none of the Lewis acids, zinc bromide, titanium tetrachloride, tin tetrachloride, or boron trifluoride etherate, induced formation of the methyleneiminium cation, and starting material was recovered. Butyraldehyde-derived intermediate **3.19b** was also utilized. Reactions of the unactivated alkene 1-hexene and cyclopentene with compound **3.19b** resulted in formation of some *N*-methylaniline, but no desired product; *N*-methylaniline arises from cleavage of the C-NPh bond instead of the C-Bt bond. When styrene was utilized, an 80% yield of desired product **3.21**, as a 1.4:1 diastereoisomeric mixture, was isolated; no *N*-methylaniline was isolated. This indicates that an equilibrium exists not only between the *N*-(*alpha*-aminoalkyl)benzotriazoles and the ions generated from rupture of the C-Bt bond, but also between the ions generated from rupture of the C-NPh bond. Furthermore, this equilibrium is shifted more towards the latter ions than the former ions by compound **3.18** possessing an electron-donating substituent on the methylene carbon. The structure of compound **3.21** was confirmed by comparison of its NMR spectra with the values reported in the literature [96SL669].

In summary, an improved method for the synthesis of 1,2,3,4-tetrahydroquinolines has been studied. The presently reported protocol has two major advantages over previously reported methods. The first one is that unactivated 1-alkenes and 1,2-disubstituted alkenes can be utilized. Second, this method can be employed for the preparation of *N*-unsubstituted and 2-substituted tetrahydroquinolines. Additionally, it

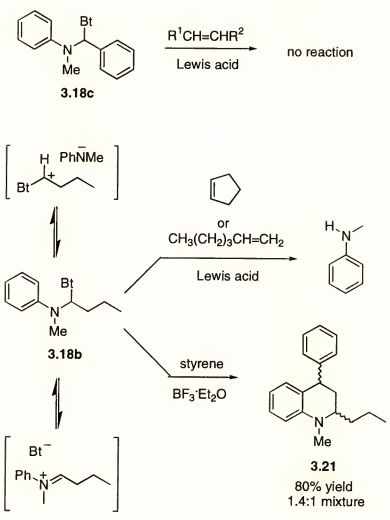


Figure 3.14. Synthesis of a 2-Substituted 1,2,3,4-Tetrahydroquinoline

was shown that the stereochemistry of the olefin was transferred stereospecifically to the product using this method. Thus, this method features wide applicability for the synthesis of 1,4-, 1,2,4-, 1,3,4- and 4-substituted tetrahydroquinolines, high yields, and utilizes readily available, crystalline *alpha*-aminoalkylbenzotriazoles as starting materials. Additionally, an interesting pattern of reactivity of *N*-(*alpha*-aminoalkyl)benzotriazoles **3.17a-c, 3.18b,c** toward olefins in the presence of Lewis acid was uncovered. First of all, compounds **3.17a-c** derived from aniline ionize readily, but are less reactive than their

analogs derived from *N*-substituted anilines. Second, an equilibrium exists not only between the *N*-(*alpha*-aminoalkyl)benzotriazoles and the ions generated from rupture of the C-Bt bond, but also with the ions generated from rupture of the C-NPh bond. This equilibrium is more towards the latter ions than the former ions when the intermediate is derived from an alkyl aldehyde **3.18b,c** rather than from formaldehyde **3.17a-c**. Lastly, the choice of Lewis acid affects not only the degree of ionization of compounds **3.17a-c, 3.18b,c**, but can also assist in the reaction of the formed methyleneiminium cation with olefins.

3.3 Experimental

3.3.1 General Comments

All melting points were measured on a hot-stage microscope and are uncorrected. NMR experiments were conducted with a Varian VXR-300 NMR spectrometer at 75 MHz for ^{13}C and 300 MHz for ^{1}H spectra. Samples were dissolved in deuteriochloroform with the internal reference being TMS (δ_H = 0.00 ppm) for ^{1}H spectra and solvent (δ_C = 77.0 ppm) for ^{13}C spectra. Elemental analyses were performed on a Carlo Erba-1106 elemental analyzer. All GC yields were determined on a HP5890 Series II Capillary GC operating in split mode with helium carrier gas and fitted with a flame ionization detector; low resolution mass spectra were recorded on a similar GC, but which was fitted to a mass selective detector (HP5972 MSD). The column used in each case was an HP5 capillary column (30 m x 0.25 mm) with a 0.25 μ film thickness of 5% phenylmethylsilicone gum. The temperature program used an initial temperature of 50 °C

for 1 min, which was then raised at a rate of 10 °C min^{-1} until 250 °C. The GC yield was determined by integration areas of all the ions detected from the GC's FID. Column chromatography was carried out using 230-400 mesh silica gel. Methylene chloride was dried over 4Å molecular sieves. Molecular sieves were activated by microwave irradiation. All other chemicals were obtained from commercial sources and were not further purified. Reactions were carried out under dry nitrogen or argon with magnetic stirring. The preparation and characterization of the *N*-(*alpha*-aminoalkyl)benzotriazoles **3.17a-c, 3.18b,c** have been published [75JCS(P1)1181, 87JCS(P1)777, 90T8153, 95JOC3993].

1-(*N*-Methyl-*N*-phenylaminomethyl)benzotriazole (**3.17a**) [75JCS(P1)1181]. The title compound was obtained as a 50:3 Bt^1:Bt^2 mixture as white rods (20:1 diethyl ether:hexanes), mp 76-77 °C (lit. mp 76-78 °C); ^{1}H NMR (minor isomer in square brackets) δ_H 8.03-7.98 (m, 1H) [7.87-7.83 (m, 2H)], 7.36-7.16 (m, 5H), 7.09-6.88 (m, 3H), 6.14 (s, 2H) [6.16 (s, 2H)], 3.02 (s, 3H) [3.31 (s, 3H)]; ^{13}C NMR δ_C 147.8, 146.2, 132.5, 129.4, 129.2, 127.4, 126.3, 123.8, 120.0, 119.8, 119.1, 118.3, 115.2, 113.7, 110.0, 72.7, 66.8, 38.8, 37.5.

1-(*N,N*-Diphenylaminomethyl)benzotriazole (**3.17b**) [87JCS(P1)777]. The title compound was obtained as colorless prisms (diethyl ether), mp 108-109 °C; ^{1}H NMR δ_H 7.97 (d, 1H, J = 7.8 Hz), 7.31-7.17 (m, 10H) 7.06 (t, 2H, J = 6.9 Hz), 6.74 (d, 1H, J = 7.5 Hz), 6.45 (s, 2H); ^{13}C NMR δ_C 146.5, 146.0, 132.8, 129.6, 127.2, 123.8, 123.3, 121.8, 119.6, 110.1, 65.3. Anal. Calcd for $C_{19}H_{16}N_4$: C, 75.98; H, 5.37; N, 18.65. Found: C, 76.03; H, 5.43; N, 18.82.

1-(*N*-Phenylaminomethyl)benzotriazole (**3.17c**) [75JCS(P1)1181]. The title compound was obtained as a 3:1 Bt^1:Bt^2 mixture as white needles (ethanol), mp 141-143 °C (lit. mp 141-143 °C); ^{1}H NMR (minor isomer in square brackets) δ_H 8.04 (d, 1H, J = 8.4 Hz) [7.86 (dd, 2H, J = 6.6, 3.0 Hz)], 7.64 (d, 1H, J = 8.4 Hz), 7.47-7.32 (m, 2H), 7.17 (t, 2H, J = 7.8 Hz), 6.92-6.77 (m, 3H), 6.08 (d, 2H, J = 6.9 Hz), [5.38 (br/t, 1H)] 5.13 (br/t, 1H); ^{13}C NMR δ_C 146.3, 144.9, 132.5, 129.5, 129.4, 127.6, 126.6, 124.2, 120.1, 119.9, 118.3, 113.9, 109.9, 64.8, 58.3.

1-[(*N*-Methyl-*N*-phenylamino)butyl]benzotriazole (**3.18b**) [90T8153]. The title compound was synthesized by shaking an equimolar mixture of butyraldehyde (20 mmol), BtH (20 mmol), and *N*-methylaniline (20 mmol) in diethyl ether with 4Å molecular sieves for 2 h; removal of volatiles afforded analytically pure product in 89% yield as a 2:1 Bt^1:Bt^2 mixture as white needles (4:1 ethyl acetate:hexanes), mp 77-79 °C (lit. mp oil); ^{1}H NMR (peaks for minor isomer in square brackets) δ_H 8.03-8.00 (m, 1H), 7.32-7.22 (m, 3H) [7.86 (dd, 2H, J = 6.5, 3.1 Hz), 7.34 (dd, 2H, J = 6.6, 3.0 Hz)], 7.09-7.04 (m, 2H), 6.94-6.80 (m, 3H), 6.41 (t, 1H, J = 7.4 Hz) [6.55 (t, 1H, J = 7.4 Hz)], 2.77 (s, 3H) [3.18 (s, 3H)], 2.63 (q, 2H, J = 7.6 Hz) [2.50-2.41 (m, 2H)], 1.58-1.44 (m, 2H) [1.40-1.18 (m, 2H)], 1.05 (t, 3H, J = 7.4 Hz) [0.99 (t, 3H, J = 7.3 Hz)]; ^{13}C NMR δ_C 149.4, 145.8, 143.9, 133.2, 129.4, 129.2, 127.1, 126.1, 123.8, 120.0, 119.7, 119.4, 118.3, 115.9, 115.0, 110.2, 80.5, 75.4, 35.4, 33.9, 32.2, 31.1, 19.3, 19.0, 13.7, 13.6. Anal. Calcd for $C_{17}H_{20}N_4$: C, 72.81; H, 7.19; N, 19.99. Found: C, 72.88; H, 7.10; N, 20.17.

1-[(*N*-Methyl-*N*-phenylamino)benzyl]benzotriazole (**3.18c**) [95JOC3993]. The title compound was synthesized by shaking an equimolar mixture of benzaldehyde (20 mmol), BtH (20 mmol), and *N*-methylaniline (20 mmol) in diethyl ether with 4Å molecular

sieves for 2 h; removal of volatiles afforded analytically pure product in 86% yield as white needles (4:1 ethyl acetate:hexanes), mp 123-126 °C (lit. mp 121-125 °C); ^{13}C NMR δ_C 148.9, 148.6, 145.8, 144.1, 136.9, 136.0, 133.0, 129.4, 129.3, 128.9, 128.8, 128.7, 128.6, 127.5, 127.2, 126.8, 126.4, 124.0, 120.1, 119.9, 119.5, 118.5, 114.9, 114.2, 110.1, 82.6, 77.2, 34.9, 34.4.

3.3.2 General Procedure for the Preparation of Tetrahydroquinolines **3.20** or **3.21** *via* Benzotriazole Derivatives **3.17a-c, 3.18b,c**

To a solution of Bt-containing compound **3.17a-c, 3.18b,c** (2 mmol), and alkene (4 mmol) in dry methylene chloride (10 mL) at 0 °C, Lewis acid (4 mmol) in dry methylene chloride (10 mL) was added under an atmosphere of argon. After being stirred for 2 h, water was added (8 mL). The layers were separated, and the aqueous layer was extracted with methylene chloride (2 x 10 mL). The combined organics were washed with brine, dried over anhydrous sodium sulfate, and evaporated to give a residue, the components of which were then separated by flash column chromatography to give the pure product. Known compounds **3.20a**-**e**, **3.20g**,**h**, **3.21** were characterized by comparison of their NMR spectral data with literature values.

4-Hexyl-1-methyl-1,2,3,4-tetrahydroquinoline (**3.20a**) [82JA5753]. The title compound was obtained as a colorless oil in 85% yield; ^{1}H NMR δ_H 7.10-6.98 (m, 2H), 6.64-6.57 (m, 2H), 3.26 (dt, 1H, J = 11.2, 4.0 Hz), 3.16-3.09 (m, 1H), 2.88 (s, 3H), 2.73-2.68 (m, 1H), 2.04-1.92 (m, 1H), 1.84-1.77 (m, 1H), 1.67-1.25 (m, 10H), 0.88 (t, 3H, J = 6.8 Hz); ^{13}C NMR δ_C 145.9, 128.4, 127.2, 127.0, 115.8, 110.8, 47.6, 38.9, 36.6, 36.2, 31.9, 29.5, 27.0, 26.4, 22.7, 14.1.

4-Butyl-1-methyl-1,2,3,4-tetrahydroquinoline (**3.20b**) [95JOC2588]. The title compound was obtained as a colorless oil in 62% yield; ^{1}H NMR δ_H 7.14-7.03 (m, 2H), 6.67-6.61 (m, 2H), 3.30 (dt, 1H, *J* = 10.8, 3.6 Hz), 3.19-3.12 (m, 1H), 2.92 (s, 3H), 2.76-2.70 (m, 1H), 2.05-1.95 (m, 1H), 1.88-1.81 (m, 1H), 1.72-1.29 (m, 6H), 0.94 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR δ_C 145.9, 128.4, 127.1, 127.0, 115.8, 110.7, 47.6, 38.9, 36.3, 36.2, 29.2, 26.4, 22.9, 14.1; MS: m/e = 203 (M^+, 26%), 146 (100).

1-Methyl-4-octyl-1,2,3,4-tetrahydroquinoline (**3.20c**) [95JOC7631]. The title compound was obtained as a colorless oil in 56% yield; ^{1}H NMR δ_H 7.10-6.99 (m, 2H), 6.64-6.58 (m, 2H), 3.26 (dt, 1H, *J* = 11.4, 4.2 Hz), 3.16-3.09 (m, 1H), 2.88 (s, 3H), 2.73-2.67 (m, 1H), 2.02-1.92 (m, 1H), 1.85-1.77 (m, 1H), 1.64-1.28 (m, 14H), 0.89 (t, 3H, *J* = 6.0 Hz); ^{13}C NMR δ_C 145.9, 128.4, 127.1, 127.0, 115.8, 110.7, 47.6, 38.9, 36.6, 36.2, 31.9, 29.8, 29.6, 29.4, 27.1, 26.4, 22.7, 14.1; MS: m/e = 259 (M^+, 26%), 146 (100).

1-Methyl-4-phenyl-1,2,3,4-tetrahydroquinoline (**3.20d**) [82JA5753]. The title compound was obtained as a colorless oil in 78% yield; ^{1}H NMR δ_H 7.08-7.32 (m, 6H), 6.75 (d, 1H, *J* = 7.4 Hz), 6.68 (d, 1H, *J* = 8.1 Hz), 6.57 (t, 1H, *J* = 7.1 Hz), 4.14 (t, 1H, *J* = 6.2 Hz), 3.22-3.16 (m, 2H), 2.94 (s, 3H), 2.27-2.22 (m, 1H), 2.13-2.07 (m, 1H); ^{13}C NMR δ_C 146.8, 146.6, 129.9, 128.6, 128.3, 127.5, 126.1, 124.8, 116.2, 111.0, 48.5, 43.4, 39.2, 31.1; MS: m/e = 223 (M^+, 100%), 208 (29), 144 (75).

1-Methyl-3,4-*cis*-propano-1,2,3,4-tetrahydroquinoline (**3.20e**) [95JCS(CC)2137]. The title compound was obtained as a colorless oil in 55% yield; ^{1}H NMR δ_H 7.11-7.04 (m, 2H), 6.71-6.63 (m, 2H), 3.03-2.91 (m, 2H), 2.83 (s, 3H), 2.68 (t, 1H, *J* = 10.5 Hz), 2.46-2.35 (m, 1H), 2.22-2.11 (m, 1H), 2.01-1.90 (m, 1H), 1.71-1.34 (m, 4H); ^{13}C NMR

δ_C 146.8, 129.4, 127.8, 126.4, 117.1, 111.4, 54.2, 41.1, 39.5, 36.2, 35.8, 29.8, 23.6; MS: m/e = 187 (M^+, 73%), 144 (100).

1-Phenyl-3,4-*cis*-propano-1,2,3,4-tetrahydroquinoline (**3.20f**). The title compound was obtained as a colorless oil in 63% yield; ^{1}H NMR δ_H 7.27-7.32 (m, 2H), 7.18-7.16 (m, 3H), 7.02 (t, 1H, *J* = 7.1 Hz), 6.92 (t, 1H, *J* = 7.5 Hz), 6.84 (d, 1H, *J* = 8.0 Hz), 7.76 (t, 1H, *J* = 7.2 Hz), 3.50 (dd, 1H, *J* = 11.8, 4.5 Hz), 3.20-3.07 (m, 2H), 2.48-2.44 (m, 1H), 2.24-2.23 (m, 1H), 1.98-1.93 (m, 1H), 1.71-1.41 (m, 4H); ^{13}C NMR δ_C 148.0, 144.1, 129.9, 129.7, 129.2, 125.8, 123.5, 122.8, 119.1, 116.1, 52.4, 41.1, 36.6, 35.7, 29.7, 23.9. Anal. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.92; H, 8.02; N, 5.83.

trans-1,3-Dimethyl-4-phenyl-1,2,3,4-tetrahydroquinoline (**3.20g**) [95JCS(CC)2137]. The title compound was obtained as white needles (diethyl ether) in 84% yield, mp 85-86 °C; ^{1}H NMR δ_H 7.32-7.21 (m, 3H), 7.12-7.06 (m, 3H), 6.67-6.60 (m, 2H), 6.52 (t, 1H, *J* = 7.2 Hz), 3.64 (d, 1H, *J* = 9.0 Hz), 3.20 (dd, 1H, *J* = 11.2, 3.8 Hz), 3.01-2.97 (m, 1H), 2.95 (s, 3H), 2.25-2.20 (m, 1H), 0.91 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR δ_C 146.5, 145.7, 130.2, 129.1, 128.2, 127.2, 126.1, 125.3, 116.4, 110.7, 56.6, 51.8, 39.3, 34.9, 18.1; MS: m/e = 237 (M^+, 100%), 222 (16), 144 (61).

cis-1,3-Dimethyl-4-phenyl-1,2,3,4-tetrahydroquinoline (**3.20h**) [95JCS(CC)2137]. The title compound was obtained as white needles (diethyl ether) in 66% yield, mp 77-78 °C; ^{1}H NMR δ_H 7.09-7.25 (m, 4H), 7.00 (d, 2H, *J* = 6.9 Hz), 6.88 (d, 1H, *J* = 7.2 Hz), 6.69 (d, 1H, *J* = 8.2 Hz), 6.55 (t, 1H, *J* = 7.4 Hz), 3.99(d, 1H, *J* = 5.0 Hz), 3.01 (d, 2H, *J* = 3.4 Hz), 2.99 (s, 3H), 2.40-2.35 (m, 1H), 0.78 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR δ_C 145.9, 142.8, 130.1, 130.0, 127.6, 125.9, 125.0, 115.9, 110.5, 53.4, 49.0, 38.7, 31.2, 16.4.

3,4-*cis*-Propano-1,2,3,4-tetrahydroquinoline (**3.20i**). The title compound was obtained as white needles (hexanes) in 20% yield, mp 43-45 °C; ^{1}H NMR δ_H 7.08 (d, 1H, J = 7.5 Hz), 6.96 (t, 1H, J = 7.5 Hz), 6.67 (t, 1H, J = 7.3 Hz), 6.54 (d, 1H, J = 8.0 Hz), 3.82 (br/s, 1H), 3.10 (dd, 1H, J = 11.0, 5.0 Hz), 2.98 (dd, 1H, J = 7.8, 6.3 Hz), 2.79 (t, 1H, J = 10.4 Hz), 2.38-2.30 (m, 1H), 2.20-2.12 (m, 1H), 2.01-1.91 (m, 1H), 1.73-1.41 (m, 4H); ^{13}C NMR δ_C 144.8, 129.9, 126.4, 126.2, 117.7, 114.6, 44.5, 40.7, 36.4, 35.3, 29.4, 23.6. Anal. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.08. Found: C, 83.46; H, 8.96; N, 8.04.

1-Methyl-4-phenyl-2-propyl-1,2,3,4-tetrahydroquinoline (**3.21**) [96SL669]. The title compound was obtained as a diastereoisomeric mixture (1.4: 1) and colorless oil in 80% yield; ^{1}H NMR δ_H 7.07-7.34 (m, 6H), 6.49-6.65 (m, 3H), 3.94-4.06 (m, 1H), 3.24-3.40 (m, 1H), 2.96 and 2.97 (s, 3H), 1.98-2.32 (m, 2H), 1.26-1.68 (m, 4H), 0.86 and 0.95 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ_C 147.3, 146.0, 144.6, 129.2, 128.7, 128.4, 127.7, 127.3, 126.4, 126.3, 125.2, 115.9, 115.3, 112.1, 110.6, 58.6, 58.5, 43.1, 40.1, 38.2, 37.3, 36.7, 36.2, 34.6, 33.8, 29.7, 19.2, 18.2, 14.3; MS: m/e = 265 (M^+, 19%), 222 (100).

CHAPTER 4
SYNTHESIS AND UTILITY OF 1-BENZOTRIAZOLYLENAMINES

4.1 Introduction

The chemistry of *alpha*-haloenamines of type **4.1** has been investigated extensively since their initial discovery 70 years ago [29MI409]. They are highly effective reagents for replacing an –OH moiety with a halogen under mild conditions (Figure 4.1) [79JCS(CC)1180, 89TL3077, 89TL3081]. *alpha*-Haloenamines have also been utilized as coupling reagents [83TL5745, 84TL4007] and as precursors for *alpha*-aminovinyl Grignard reagents of type **4.2** [72AGE852, 76AGE371]. Furthermore, they are versatile synthetic intermediates for functionalized amides of type **4.3** [69AGE454, 79JA4381], enamines of type **4.4** [69AGE454], 2-amino-1-azirines of type **4.5** [70TL3765], cyclobutenones of type **4.6** [75AGE569], cyclobutanones [81S706], azetidinones [84JOC1397], and numerous other classes of compounds [98T9207]. Although the synthesis of *alpha*-haloenamines is reasonably easy, these compounds, especially those with only one substituent at the 2-position, are unstable and require special handling [88MI282].

Recently, *alpha*-triflyloxyenamines of type **4.8** have been successfully synthesized and used in further transformations [99JA593, 97JOC8131, 97JOC3592, 95JOC2656]. For example, sequential treatment of lactam **4.7** with potassium bis(trimethylsilyl)amide (KHMDS) and *N*-(5-chloro-2-pyridinyl)triflimide afforded compound **4.8** (Figure 4.2).

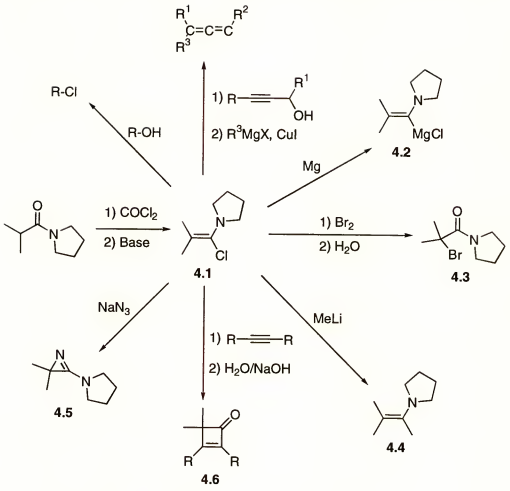


Figure 4.1. Utility of 1-Chloroenamines

This intermediate then underwent reaction with methyl cuprate and a variety of palladium-catalyzed coupling reactions. Thus, there is an interest in enamines with leaving groups other than halogen in the *alpha*–position. The Bt moiety can behave similarly to halogen substituents, but Bt derivatives are typically more stable and less reactive than their halogen analogs [98CRV409]. *alpha*-(Benzotriazolyl)alkylamines of type **4.9** or **4.10** are well recognized synthetic intermediates which have been used in further reactions with nucleophiles [89JCS(P1)225]. In addition to the Reformatsky reaction discussed in Chapter 2, the Bt group of *alpha*-(benzotriazolyl)alkylamines has

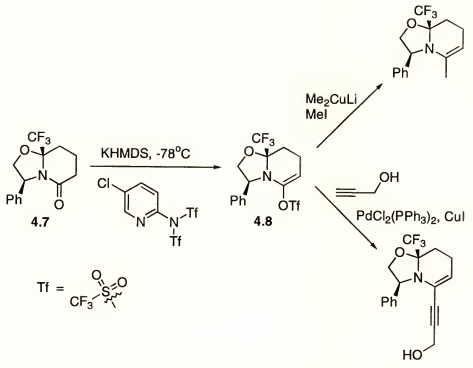


Figure 4.2. Utility of a 1-Triflyloxyenamine

been displaced by reaction with $NaBH_4$ and Grignard reagents (Figure 4.3). In this context, our attention was drawn to the potential of *alpha*-benzotriazolylenamines.

Two previous publications from our group [90CB1545, 95H131] each describe a single example of *alpha*-benzotriazolylenamines, but their chemistry was not further explored. In connection with the preparation of imidoylbenzotriazoles from aliphatic carboxylic acids [90CB1545], we previously showed that the action of BtH (4 equiv), $POCl_3$ (2 equiv), and triethylamine (2 equiv) on benzamide at 0 °C gave benzonitrile in 87% yield. Under the same conditions, *N*-methyl-*N*-phenyloctanamide (**4.11**) gave *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-1-octenyl]-*N*-methylaniline (**4.12**) as a mixture of E and Z isomers in 70% yield (Figure 4.4). The other *alpha*-benzotriazolylenamine was prepared during an investigation into the lithiation of various *N*-substituted benzotriazoles

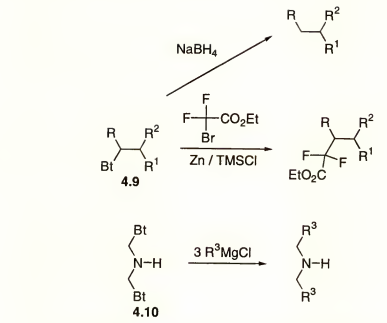


Figure 4.3. Displacement of a Benzotriazolyl Group

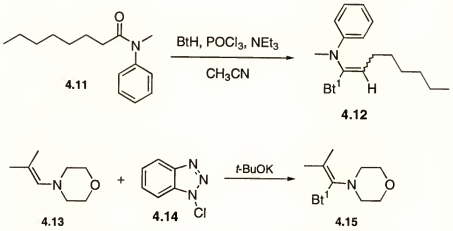


Figure 4.4. Syntheses of 1-Benzotriazolylenamines

[95H131]. 1-(1*H*-1,2,3-Benzotriazol-1-yl)-morpholino-2-methylpropene (**4.15**) was synthesized in 37% yield from the sequential treatment of 1-morpholino-2-methyl-1-propene (**4.13**) with 1-chloro-1*H*-1,2,3-benzotriazole (**4.14**) and potassium *t*-butoxide at

low temperature (Figure 4.4). The present study intends to further explore the scope and limitations of *alpha*-benzotriazolylenamines as stable analogs of *alpha*-haloenamines.

4.2 Results and Discussion

4.2.1 Preparation of Amides **4.16a-g**

All amides **4.16a-g** were synthesized in 65 – 89% yield using the procedure of Human and Mills (Figure 4.5, Table 4.1) [46NAT877]. More specifically, pyridine (20 or 50 mmol) was added to a diethyl ether solution of an aliphatic acid (1 equiv). After 5 min in an ice water bath, thionyl chloride (1 equiv) was added dropwise to the reaction vessel. After 5 min, a mixture of pyridine (1 equiv) and aniline derivative (1 equiv) was then added dropwise to the reaction vessel. The ice bath was removed, and the mixture stirred for 2 h at rt. Successive washes with 2N $HCl_{(aq)}$ (3 x 100 mL), 10% $NaOH_{(aq)}$ (3 x 50 mL), and brine (50 mL) gave, after reduced-pressure removal of volatiles, analytically pure product. This procedure worked well for amides **4.16a-d,f,g**; however, compound **4.16e** had to be recrystallized from ethyl acetate. An attempt to make the amide from octanoic acid and carbazole failed, possibly due to the poor solubility of carbazole in the solvent system.

Amides **4.16a-c,f,g** have been synthesized previously; their spectra and physical properties were consistent with those reported in the literature and with the proposed structure (see Experimental section). *N*-Ethyl-*N*-phenylhexanamide (**4.16d**) and *N,N*-diphenylhexanamide (**4.16e**) gave satisfactory elemental analysis and NMR spectra. The ^{1}H NMR spectrum of compound **4.16d** integrated for the 5 aromatic protons [δ_H 7.45-

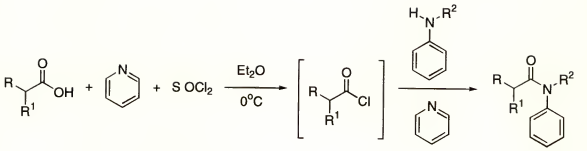


Figure 4.5. Synthesis of Amides

Table 4.1. Synthesis of Amides **4.16a-g**

4.16	R	R^1	R^2	Yield (%)
a	Et	H	Me	73
b	*t*-Bu	H	Me	65
c	Bu	H	Me	78
d	Bu	H	Et	74
e	Bu	H	Ph	81
f	Ph	H	Me	89
g	Me	Me	Me	88

7.32 (m, 3H), 7.16 (d, 2H, J = 7.4 Hz)], the 2-proton quartet of the *N*-ethyl group [δ_H 3.76 (J = 7.1 Hz)], the 2-proton triplet of the CH_2CO unit [δ_H 2.02 (J = 7.7 Hz)], the 3-proton triplet of the alkyl chain's methyl group [δ_H 0.82 (J = 7.2 Hz)], and 9 other protons as multiplets [δ_H 1.62-1.52 (2H), 1.26-1.03 (7H)]. The ^{13}C NMR spectrum contained a signal for the carbonyl group (δ_C 172.1), 4 aromatic signals (δ_C 142.1, 129.2, 128.0, 127.4), and 7 aliphatic signals (δ_C 43.5, 33.9, 31.0, 24.8, 21.9, 13.4, 12.6) as expected. The ^1H NMR spectrum for amide **4.16e** showed signals for the 2 benzene rings [δ_H 7.42-7.14 (m, 10H)], the CH_2 *alpha* to the carbonyl [δ_H 2.25 (t, 2H, J = 7.4 Hz)], the internal alkyl groups [δ_H 1.73-1.58 (m, 2H), 1.32-1.16 (m, 4H)], and the terminal CH_3 group [δ_H

0.85 (t, 3H, J = 6.5 Hz)]. The ^{13}C NMR spectrum for compound **4.16e** contained the expected resonances for the carbonyl group (δ_C 173.2) and the aliphatic carbons (δ_C 35.1, 31.2, 25.1, 22.2, 13.8), but the aromatic region contained only 2 clear peaks (δ_C 142.8, 129.1) along with a very broad signal (δ_C 130.5-124.8) instead of the pair of peaks expected for the *ortho* and *meta* carbons of the aromatic rings.

4.2.2 Preparation of Enamine **4.19**

Although there are several excellent reports on the preparation of enamines [79TL2433, 82T1975, 88MI1], syntheses of enamines formally derived from an aliphatic aldehyde unbranched in the 2-position and an *N*-alkylaniline are quite rare. Some methods, such as the synthesis of *N*-methyl-*N*-vinylaniline by elimination of dimethylammonium bromide from trimethyl-[2-(*N*-methylanilino)ethyl]ammonium bromide [19CB2261] or *N*-methyl-*N*-(1-propenyl)aniline by isomerization of *N*-allyl-*N*-methylaniline [68BSF4430], are quite limited in scope. Two methods that appear to be potentially general in nature were found in the literature, although only one example was reported to be synthesized by each method. In the first method [80TL2671], an *N*-(alkoxymethyl)-*N*-methylaniline undergoes an Arbuzov reaction with Ph_2PCl to give *N*-methyl-*N*-anilinomethyl diphenylphosphine oxide **4.17** (Figure 4.6). Compound **4.17** is then lithiated at low temperature and treated with aldehyde to give compound **4.18**. Subsequent treatment of compound **4.18** with base gives an enamine. This multistep sequence requires extreme conditions, and therefore was not utilized.

The second method entailed (1) the reaction of BtH (50 mmol), butyraldehyde (1 equiv), and *N*-methylaniline (1 equiv) in diethyl ether at rt for 4.5 h, (2) reduced-pressure

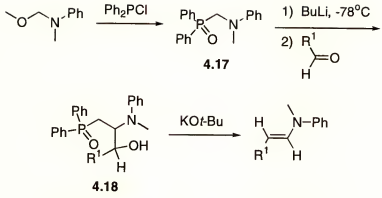


Figure 4.6. Indirect Synthesis of an Enamine

removal of volatiles, (3) reaction of this crude product for 3 h with NaH in refluxing THF and (4) distillation of the pure product **4.19** [90T8153]. Using this method, enamine **4.19** was synthesized in 18% isolated yield (Figure 4.7). The NMR spectra of enamine **4.19** clearly indicated an buten-1-yl group with trans stereochemistry [δ_H 6.67 (d, 1H, J = 13.4 Hz), 4.68 (m, 1H), 2.09 (m, 2H), 1.03 (t, 3H, J = 7.4 Hz); δ_C, 132.3, 106.1, 23.7, 15.8]

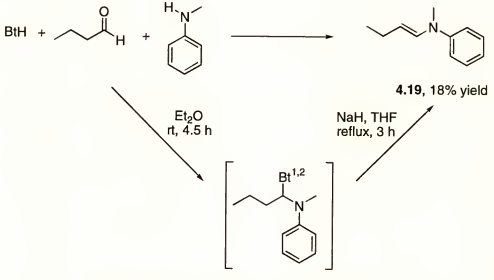


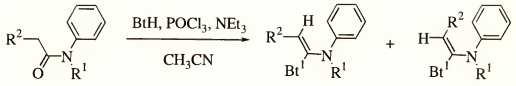
Figure 4.7. Direct Synthesis of an Enamine

and an *N*-methyl-*N*-phenyl moiety [δ_H 7.22-6.81 (m, 5H), 3.05 (s, 3H); δ_C 147.8, 129.0, 119.5, 116.1, 34.8].

4.2.3 Preparation of *alpha*-Benzotriazolylenamines **4.20a-g**, **4.21a-f,** and **4.22a,b**

The reaction of BtH and $POCl_3$ with an amide for the synthesis of *alpha*-benzotriazolylenamines has now been explored and extended. In a typical procedure, BtH (4 equiv), $POCl_3$ (2 equiv), NEt_3 (2 equiv), and tertiary amide (5 mmol) were sequentially added dropwise as solutions in acetonitrile to a nitrogen-blanketed round-bottomed flask at rt (Figure 4.8). Disappearance of the amide was monitored by TLC or GC. The reactions which made compounds **4.20a,c,d, 4.21a,c,d** were performed over 14 h at rt, but refluxing was required for the rapid synthesis of compounds **4.20g, 4.22a** (2 d), **4.20e,f, 4.21e,f** (3 d) and **4.20b, 4.21b** (10 d). The reaction was worked-up as described in the experimental section once no amide was left in the reaction mixture.

The desired *alpha*-benzotriazolylenamines **4.20** and **4.21** were typically isolated in good combined yields (53-88%) as separated Z **4.20a-e** and E **4.21a-e** isomers (Table 4.2); structure elucidation is discussed on page 94. Exceptionally, *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2-methylprop-1-enyl]-*N*-methylaniline (**4.20g**, 74%) can only exist as one isomer (Figure 4.9) and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2-phenyleth-2-enyl]-*N*-methylaniline (**4.20f/4.21f**, 56%) was isolated as an E/Z mixture (ca 10:1) by flash column chromatography. Traces of what could have been Bt^2 isomers **4.22** were detected in the MS of the crude reaction mixture starting from each amide **4.16a-g**. However, compound **4.22a** was the only Bt^2 isomer isolated using this method, this being from the reaction mixture of *N*,2-dimethyl-*N*-phenylbutanamide (**4.16e**).

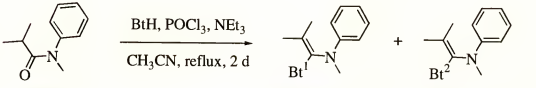


4.16 **4.20** **4.21**

Figure 4.8. Synthesis of 1-Benzotriazolylenamines From Amides

Table 4.2. Synthesis of 2-Substituted-1-(benzotriazol-1-yl)enamines **4.20a-f**, **4.21a-f** From Amides **4.16a-f**

Amide **4.16**	Conditions	Time	R^1	R^2	Product (% yield)
a	rt	14 h	Me	Et	**4.20a** (25) and **4.21a** (63)
b	reflux	10 d	Me	*t*-Bu	**4.20b** (17) and **4.21b** (36)
c	rt	14 h	Me	Bu	**4.20c** (21) and **4.21c** (58)
d	rt	14 h	Et	Bu	**4.20d** (31) and **4.21d** (53)
e	reflux	3 d	Ph	Bu	**4.20e** (18) and **4.21e** (53)
f	reflux	3 d	Me	Ph	**4.20f** and **4.21f** (56)



4.16g **4.20g** (74% yield) **4.22a** (1% yield)

Figure 4.9. Synthesis of a 2,2-Disubstituted 1-Benzotriazolylenamine

In a reinvestigation of the synthesis of *alpha*-benzotriazolylenamines from enamines, it was found that when *N*-(*trans*-buten-1-yl)-*N*-methylaniline (**4.19**) was sequentially reacted with 1-chloro-1*H*-1,2,3-benzotriazole (**4.14**) and *t*-BuOK in diethyl ether at –38 °C (acetonitrile-dry ice bath) a 52% yield of a 2:1 mixture of *N*-[(*Z*)-1-(1*H*-1,2,3-benzotriazol-1-yl)-1-butenyl]-*N*-methylaniline (**4.20a**) and *N*-[(*E*)-1-(2*H*-1,2,3-benzotriazol-2-yl)-1-butenyl]-*N*-methylaniline (**4.22b**) isomers was obtained (Figure

4.10). Isomers **4.20a** and **4.22b** were isolated as separate compounds by silica gel, flash column chromatography. Further exploration of this method was not pursued because the amide method gave superior yields under less extreme conditions.

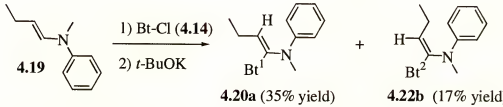


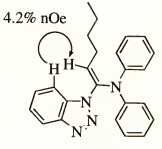
Figure 4.10. Synthesis of 1-Benzotriazolylenamines From an Enamine

4.2.4 Characterization of *alpha*-Benzotriazolylenamines **4.20a-g, 4.21a-f,** and **4.22a,b**

alpha-Benzotriazolylenamines **4.20a-g**, **4.21a-f** and **4.22a,b** were all characterized by elemental analysis and by their ^{1}H and ^{13}C NMR spectra. For example, *N*-[(*Z*)-1-(1*H*-1,2,3-benzotriazol-1-yl)-1-butenyl]-*N*-methylaniline (**4.20a**) showed the expected carbon resonances for the Bt^{1} moiety [δ_C 145.4 (C3a), 132.7 (C7a), 127.9 (C6), 124.0 (C5), 121.0 (C4), 110.8 (C7) ppm], the *N*-phenyl group [δ_C 146.8 (C1), 129.0 (C2), 119.9 (C4), 117.8 (C3) ppm], the double bond [137.0 (C) and 119.2 (CH) ppm], the *N*-CH_3 (δ_C 38.8 ppm), and the alkyl group [δ_C 20.5 (CH_2) and 14.3 (CH_3) ppm]. Similarly, the proton resonances for both the Bt and *N*-monosubstituted-phenyl moieties in the aromatic region, a 1-proton triplet (δ_H 5.52 ppm, J = 7.6 Hz) in the olefinic region, and an *N*-CH_3 singlet (δ_H 3.10 ppm), a CH_2 multiplet (δ_H 2.13-2.03 ppm), and a CH_3 triplet (δ_H 1.04, J = 7.6 Hz) in the aliphatic region were observed. The fact that there was coupling between the CH_2 of the ethyl group (δ_H 2.13-2.03 ppm) and the vinylic proton (δ_H 5.52 ppm) of

compound **4.20a** and that this coupling was absent in *N*-[(*Z*)-1-(1*H*-1,2,3-benzotriazol-1-yl)-3,3-dimethylbut-1-enyl]-*N*-methylaniline (**4.20b**) are evidence that the vinylic proton is attached to the same carbon of the double bond as the alkyl fragment derived from the acid portion of the amide.

When C2 has an attached proton as in compounds **4.20a-f**, **4.21a-f** and **4.22b**, both *alpha*-Bt^1- and *alpha*-Bt^2-enamines could exist as either E or Z isomers. Stereochemistry of the Bt^1 compounds was assigned based on the fact that irradiation of the C7 proton of the Bt^1 moiety (δ_H 7.74 ppm) of *N*-[(*E*)-1-(1*H*-1,2,3-benzotriazol-1-yl)-1-hexenyl]-*N*-methylaniline (**4.21e**) gave a small (4.2%) positive nOe for the vinylic proton (δ_H 5.94 ppm), establishing a cisoid relationship between these two groups in this compound (Figure 4.11). For the Bt^1 isomers (Table 4.3), the vinylic proton consistently appeared at either δ_H ~6.0 ppm for the E or δ_H ~5.5 ppm for the Z isomer in each pair of products from an amide. Due to this consistency in the chemical shift of the two isomers, and the fact that the stereochemistry of compound **4.21e** (δ_H 5.94 ppm) was confirmed as E by an nOe experiment, it was concluded that all such Bt^1 isomers with δ_H ~6.0 ppm (**4.21a-e**) had E stereochemistry and those with δ_H ~5.5 ppm (**4.20a-e**) had Z stereochemistry.



4.21e

Figure 4.11. Results From an nOe Experiment on a 1-Benzotriazolylenamine

Table 4.3. ^{1}H NMR Data for Vinylic Protons of Compounds **4.20a-e**, **4.21a-e**

4.20	C=C*H* (δ_H ppm) [multiplicity]	**4.21**	C=C*H* (δ_H ppm) [multiplicity]
a	5.52 [t]	**a**	5.98 [t]
b	5.62 [s]	**b**	6.01 [s]
c	5.53 [t]	**c**	5.99 [t]
d	5.56 [t]	**d**	6.01 [t]
e	5.57 [t]	**e**	5.94 [t]

It was observed that *N*-[(*E*)-1-(2*H*-1,2,3-benzotriazol-2-yl)-1-butenyl]-*N*-methylaniline (**4.22b**) isomerized upon storage. After 1 month in $CDCl_3$, the ^{1}H NMR of a sample of compound **4.22b**, which initially displayed a triplet for the vinylic proton at δ_H 6.62 ppm, displayed triplets at δ_H 6.62, 5.70, and 5.52 ppm. The signal at δ_H 5.52 ppm was assigned to the Z-Bt^1 isomer **4.20a**, indicating that the Bt^2 compounds can isomerize into the Bt^1 isomers. Since the Bt^1 compounds with the more shielded vinylic signals (δ_H ~6.0 ppm, **4.21a-e**) had E stereochemistry while the others (δ_H ~5.5 ppm, **4.20a-e**) had Z stereochemistry, Bt^2 compound **4.22b** (δ_H 6.62 ppm) was assigned E stereochemistry and the signal at (δ_H 5.70 ppm) was assigned to the vinylic proton of the corresponding Z-Bt^2 isomer. The E and Z isomers derived from the Bt^2 compound **4.22b** could not be separated. *N*-[1-(2*H*-1,2,3-Benzotriazol-2-yl)-2-methyl-1-propenyl]-*N*-methylaniline (**4.22a**) was characterized by elemental analysis (± 0.2%) and ^{1}H and ^{13}C NMR spectroscopy. Its NMR spectra were similar to those of compound **4.20g**, except for the expected differences between Bt^2 and Bt^1 compounds.

4.2.5 Stability of *alpha*-Benzotriazolylenamines **4.20a-g** and **4.21a-f**

The Bt^1 isomers did not interconvert at ambient conditions either neat or in solution. This was demonstrated by finding the NMR spectra of pure samples, compounds **4.20a** and **4.21a** in colorless, translucent, topless vials and deuteriochloroform solutions of compounds **4.20c** and **4.21c** in colorless, translucent open-ended NMR tubes, unchanged after 2 months on a laboratory bench. Since the Bt^2 compounds unidirectionally isomerize into the Bt^1 compound, it can be concluded that the Bt^1 isomers are thermodynamically more stable than their Bt^2 analogs. Additionally, compounds **4.20a-g**, **4.21a-f** and **4.22a** did not decompose under acidic ($POCl_3$) reaction conditions, basic (saturated, aqueous K_2CO_3) work-up, or silica gel column chromatography. Compounds **4.20a** and **4.22b**, which were made by reaction of enamine **4.19** with compound **4.14**, were stable to basic reaction conditions (*t*-BuOK) and silica gel column chromatography.

4.2.6 Limitations to the Preparation of *alpha*-Benzotriazolylenamines **4.20** and **4.21** From Amides **4.16**

Although the synthesis of *alpha*-benzotriazolylenamines tolerated alkyl (**4.16a-e,g**) and aryl (**4.16f**) groups as well as linear (**4.16a,c-e**) and branched (**4.16b,f,g**) groups on the acid portion of the amide, the amine portion of the amide had to be a tertiary aniline derivative. Thus, *N*-methyl-2-pyrrolidinone, *N,N*-dimethylpropionamide, and 1-acetylpiperidine did not yield any *alpha*-benzotriazolylenamine (Figure 4.12). In addition to the reaction with 1-acetylpiperidine, the use of acetamides, namely *N*-methylacetanilide and

N-phenylacetanilide, failed to give any desired 1-benzotriazolylenamine. Starting amide was recovered using CH_2Cl_2 or THF as solvent, instead of acetonitrile.

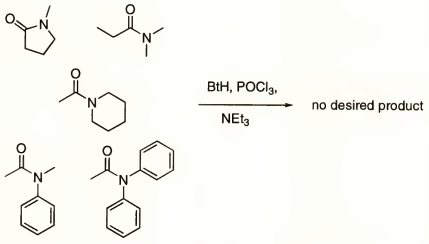


Figure 4.12. Amides Not Giving 1-Benzotriazolylenamines

Additionally, the use of 1-(trimethylsilyl)-1*H*-1,2,3-benzotriazole (**4.23**) instead of BtH in the reaction of *N*-methyl-*N*-phenylbutanamide (**4.16a**) under optimized conditions produced the transamination product **4.24** in 46% yield (Figure 4.13) as the major product without any *alpha*-benzotriazolylenamine being formed, as determined by GC/MS of the crude reaction mixture. The identity of compound **4.24** was confirmed by comparing its NMR spectra and melting point with those found in the literature

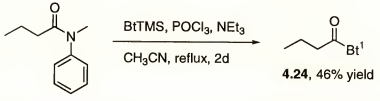


Figure 4.13. Use of Bt-TMS Instead of Bt-H in Reaction With an Amide

[96MI881]. In other attempts to discover a supplementary method to *alpha*-benzotriazolylenamines (Figure 4.14), an amide (2mmol) in THF was treated with strong base (1 equiv) at –78 °C (acetone-dry ice bath) followed by 1-[(4-methylphenyl)sulfonyl]-1*H*-1,2,3-benzotriazole (**4.25**, BtTs, 1 equiv). The reaction mixture was allowed to warm to rt before a basic workup. Specifically, *N*-methyl-2-pyrrolidinone was treated with n-butyllithium as base, while *N*,*N*-dimethylpropionamide and *N*-methylacetanilide were each treated with LDA as base; greater than 70% of the amide was recovered in each case.

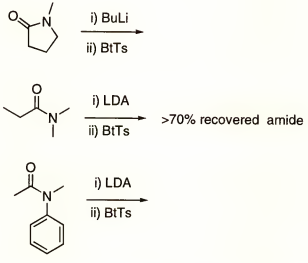


Figure 4.14. Unsuccessful Method to 1-Benzotriazolylenamines

4.2.7 Reaction of *alpha*-Benzotriazolylenamines **4.20a** and **4.22a** With Organozinc Reagents

Similar to the displacement of chloride from *N*-(1-chloro-2-methylpropyl)piperidine by phenylmagnesium bromide (70% yield) [69AGE454], *N*-[1-

(2*H*-1,2,3-benzotriazol-2-yl)-2-methylprop-1-enyl]-*N*-methylaniline (**4.22a**) readily underwent nucleophilic substitution of the Bt moiety by phenylethynylzinc chloride, and was thereby converted in 76% yield into *N*-methyl-*N*-[2-methyl-1-(2-phenylethynyl)-1-propenyl] aniline (**4.26**) (Figure 4.15). Compound **4.26** was characterized by NMR spectroscopy. The ^{1}H NMR showed a 10-proton integration in the aromatic region, a 3-proton singlet at δ_H 3.01 typical for an *N*-CH_3 group and two 3-proton singlets further upfield (δ_H 2.07 and 1.73 ppm) which correspond to the allylic methyl groups. The ^{13}C NMR showed signals that reaffirmed those from the ^{1}H NMR spectrum in addition to two quaternary signals expected from the presence of the triple bond (δ_C 90.7, 86.0 ppm); no signals characteristic of a Bt group were detected.

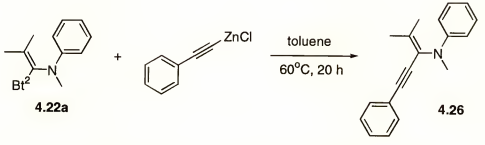


Figure 4.15. Displacement of Bt From a 1-Benzotriazolylenamine

Pure products were not obtained from reactions of 2-unsubstituted-1-(benzotriazol-1-yl)enamines with other organozinc reagents (Figure 4.16). The crude reaction mixture of each reaction gave mass spectra of a single species with m/e appropriate to the desired products, but silica gel flash column chromatography or distillation failed to give expected product. Such enamines are known to be quite reactive and tend to undergo self-condensation at even moderate temperatures (over 60 °C) [80JCS(P1)2732]. More

specifically, the reaction of *N*-[(*Z*)-1-(1*H*-1,2,3-benzotriazol-1-yl)-1-butenyl]-*N*-methylaniline (**4.20a**) with phenylethynylzinc chloride (2 equiv) in toluene at 60°C for 8 h gave an 87% GC/MS yield (excluding organozinc dimer) of m/e = 261, but no compounds were isolated by silica gel chromatography. When methylzinc chloride (2 equiv) was reacted with compound **4.20a** (5 mmol) at 60 °C for 2 d in toluene, GC/MS showed unreacted starting material. The same reaction gave a 46% GC/MS yield of m/e = 165 after 6 h at 80 °C, but no expected product was isolated by vacuum distillation.

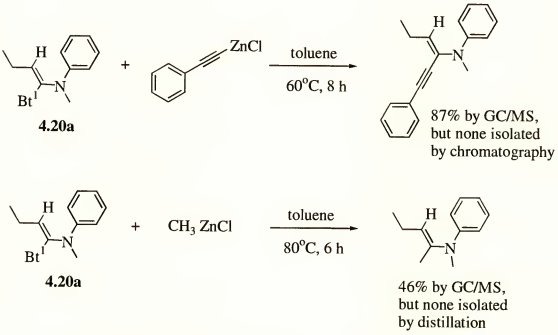


Figure 4.16. Other Displacements of Bt From 1-Benzotriazolylenamines

In conclusion, the earlier work in this group [90CB1545, 95H131] on the synthesis of *alpha*-benzotriazolylenamines was further explored in order to ascertain the scope and limitations of these syntheses and to demonstrate the potential utility of *alpha*-benzotriazolylenamines as stable analogs to *alpha*-chloroenamines. A variety of *alpha*-

(benzotriazol-1-yl)enamines **4.20a-g**, **4.21a-f** and **4.22a** were easily prepared as separated E and Z isomers, except for the mixture of compound **4.20f/4.21f**, in good overall yields from amides **4.16a-g** using BtH, $POCl_3$ and NEt_3. The amides **4.16a-g** were readily synthesized in excellent purity from reactions of acids with aniline derivatives by action of thionyl chloride and pyridine. Additionally, *N*-[(*E*)-1-(2*H*-1,2,3-benzotriazol-2-yl)-1-butenyl]-*N*-methylaniline (**4.22b**) was synthesized along with *N*-[(*Z*)-1-(1*H*-1,2,3-benzotriazol-1-yl)-1-butenyl]-*N*-methylaniline (**4.20a**) in moderate yield by reaction of *N*-(*trans*-buten-1-yl)-*N*-methylaniline (**4.16**) with 1-chloro-1*H*-1,2,3-benzotriazole (**4.14**) and *t*-BuOK. The utility of these stable compounds was demonstrated by the nucleophilic substitution of the benzotriazolyl moiety from compound **4.22a** by phenylethynylzinc chloride to form *N*-methyl-*N*-[2-methyl-1-(2-phenylethynyl)-1-propenyl]aniline (**4.26**).

4.3 Experimental

4.3.1 General Comments

All melting points were measured on a hot-stage microscope and are uncorrected. NMR experiments were conducted with a Varian VXR-300 NMR spectrometer at 75 MHz for ^{13}C and 300 MHz for ^{1}H spectra. Samples were dissolved in deuteriochloroform with the internal reference being TMS ($\delta_H = 0.00$ ppm) for ^{1}H spectra and solvent ($\delta_C =$ 77.0 ppm) for ^{13}C spectra. Elemental analyses were performed on a Carlo Erba-1106 elemental analyzer. Prior to use, acetonitrile was distilled from CaH_2, diethyl ether and THF were distilled from sodium/benzophenone, and toluene was distilled from sodium. Column chromatography was carried out using 230-400 mesh silica gel. All other

chemicals were obtained from commercial sources and were not further purified. Reactions were carried out under dry nitrogen or argon with magnetic stirring.

N-(*trans*-Buten-1-yl)-*N*-methylaniline (**4.19**) was prepared by the literature method in 18% yield [90T8153]. 1-Chloro-1*H*-1,2,3-benzotriazole (**4.14**) [69JCS(CC)1474], 1-(trimethylsilyl)-1*H*-1,2,3-benzotriazole (**4.23**) [68JHC785] and 1-[(4-methylphenyl) sulfonyl]-1*H*-1,2,3-benzotriazole (**4.25**) [65CB3142] were prepared in accordance with the literature method.

N-(*trans*-Buten-1-yl)-*N*-methylaniline (**4.19**) [90T8153]. The title compound was obtained as a yellow oil, 18%; ^{1}H NMR δ_H 7.22-6.81 (m, 5H), 6.67 (d, 1H, J = 13.4 Hz), 4.68 (m, 1H), 3.05 (s, 3H), 2.09 (m, 2H), 1.03 (t, 3H, J = 7.4 Hz); ^{13}C NMR δ_C 147.8, 132.3, 129.0, 119.5, 116.1, 106.1, 34.8, 23.7, 15.8.

1-Chloro-1*H*-1,2,3-benzotriazole (**4.14**) [69JCS(CC)1474]. The title compound was obtained as white needles (ethyl acetate), mp 103-105 °C (lit mp 104-106 °C), 87%; ^{1}H NMR δ_H 8.07 (d, 1H, J = 8.4 Hz), 7.65-7.55 (m, 2H), 7.51-7.42 (m, 1H); ^{13}C NMR δ_C 143.7, 133.7, 129.0, 124.8, 120.2, 109.0.

1-(Trimethylsilyl)-1*H*-1,2,3-benzotriazole (**4.23**) [68JHC785]. The title compound was obtained as a yellow oil, 88%; ^{1}H NMR δ_H 8.14 (d, 1H, J = 8.3 Hz), 7.65 (d, 1H, J = 8.3 Hz), 7.47 (t, 1H, J = 7.2 Hz), 7.38 (t, 1H, J = 7.4 Hz), 0.71 (s, 9H); ^{13}C NMR δ_C 146.7, 137.8, 127.0, 123.4, 119.8, 111.1, -0.45.

1-[(4-Methylphenyl)sulfonyl]-1*H*-1,2,3-benzotriazole (**4.25**) [65CB3142]. The title compound was obtained as white needles (ethyl acetate), mp 133-134 °C (lit mp 135 °C), 78%; ^{1}H NMR δ_H 8.11 (d, 1H, J = 8.5 Hz), 8.06 (d, 1H, J = 8.5 Hz), 7.99 (d, 2H, J = 7.9 Hz), 7.66 (t, 1H, J = 7.6 Hz), 7.47 (t, 1H, J = 7.6 Hz), 7.31 (d, 2H, J = 7.7 Hz), 2.38 (s,

3H); ^{13}C NMR δ_C 146.7, 145.3, 133.9, 131.5, 130.2, 130.1, 127.8, 125.7, 120.4, 111.9, 21.6.

4.3.2 Preparation of Amides **4.16a-g**

All amides were synthesized in good yields using the procedure of Human and Mills, which delivers pure compounds [46NAT877]. Pyridine (20 or 50 mmol) was added to a diethyl ether solution of an aliphatic acid (1 equiv). After 5 min in an ice water bath, thionyl chloride (1 equiv) was added dropwise to the reaction vessel. After 5 min, a mixture of pyridine (1 equiv) and aniline derivative (1 equiv) was then added dropwise to the reaction vessel. The ice bath was removed, and the mixture stirred for 2 h at rt. Successive washes with 2N $HCl_{(aq)}$ (3 x 100 mL), 10% $NaOH_{(aq)}$ (3 x 50 mL), and brine (50 mL) gave, after reduced-pressure removal of volatiles, analytically pure product. Syntheses of *N*-methyl-*N*-phenylbutanamide (**4.16a**) [61JA4549], *N*,3,3-trimethyl-*N*-phenylbutanamide (**4.16b**), *N*-methyl-*N*-phenylhexanamide (**4.16c**), *N*-methyl-*N*,2-diphenylacetamide (**4.16f**) [91JOC4218], and *N*,2-dimethyl-*N*-phenylpropanamide (**4.16g**) [83HCA262] by alternative methods have been reported.

N-Methyl-*N*-phenylbutanamide (**4.16a**) [61JA4549]. The title compound was obtained as a yellow oil, 73%; ^{1}H NMR δ_H 7.45-7.34 (m, 3H), 7.18 (d, 2H, J = 7.4 Hz), 3.28 (s, 3H), 2.06 (t, 2H, J = 7.1 Hz), 1.66-1.53 (m, 2H), 0.83 (t, 3H, J = 7.3 Hz); ^{13}C NMR δ_C 172.8, 144.1, 129.5, 127.4, 127.1, 37.0, 35.8, 18.7, 13.6.

N,3,3-Trimethyl-*N*-phenylbutanamide (**4.16b**) [95HCA1983]. The title compound was obtained as a yellow oil, 65%; ^{1}H NMR δ_H 7.43-7.28 (m, 3H), 7.15 (d, 2H, J = 7.4

Hz), 3.26 (s, 3H), 2.05 (s, 2H), 0.96 (s, 9H); ^{13}C NMR δ_C 171.8, 144.6, 129.4, 127.4, 127.3, 45.3, 37.2, 31.2, 29.7.

N-Methyl-*N*-phenylhexanamide (**4.16c**) [97SL812]. The title compound was obtained as white rods (chloroform), mp 96-97 °C (lit mp, oil), 78%; ^{1}H NMR δ_H 7.44-7.33 (m, 3H), 7.18 (d, 2H, J = 7.2 Hz), 3.27 (s, 3H), 2.07 (t, 2H, J = 7.2 Hz), 1.60-1.55 (m, 2H), 1.23-1.18 (m, 4H), 0.83 (t, 3H, J = 6.8 Hz); ^{13}C NMR δ_C 173.2, 144.2, 129.6, 127.5, 127.2, 37.2, 33.9, 31.4, 25.1, 22.3, 13.8.

N-Ethyl-*N*-phenylhexanamide (**4.16d**). The title compound was obtained as a colorless oil, 74%; ^{1}H NMR δ_H 7.45-7.32 (m, 3H), 7.16 (d, 2H, J = 7.4 Hz), 3.76 (q, 2H, J = 7.1 Hz), 2.02 (t, 2H, J = 7.7 Hz), 1.62-1.52 (m, 2H), 1.26-1.03 (m, 7H), 0.82 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ_C 172.1, 142.1, 129.2, 128.0, 127.4, 43.5, 33.9, 31.0, 24.8, 21.9, 13.4, 12.6. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.38; H, 9.92; N, 6.61.

N, N-Diphenylhexanamide (**4.16e**). The title compound was obtained as white rods (ethyl acetate), mp 42-44 °C, 81%; ^{1}H NMR δ_H 7.42-7.14 (m, 10H), 2.25 (t, 2H, J = 7.4 Hz), 1.73-1.58 (m, 2H), 1.32-1.16 (m, 4H), 0.85 (t, 3H, J = 6.5 Hz); ^{13}C NMR δ_C 173.2, 142.8, 129.1, 130.5-124.8/br, 35.1, 31.2, 25.1, 22.2, 13.8. Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.86; H, 8.23; N, 5.25.

N-Methyl-*N*,2-diphenylacetamide (**4.16f**) [91JOC4218]. The title compound was obtained as a yellow oil, 89%; ^{1}H NMR δ_H 7.38-7.04 (m, 10H), 3.45 (s, 2H), 3.26 (s, 3H); ^{13}C NMR δ_C 170.7, 143.8, 135.2, 129.5, 128.8, 128.1, 127.7, 127.4, 126.3, 40.7, 37.4.

N,2-Dimethyl-*N*-phenylpropanamide (**4.16g**) [83HCA262]. The title compound was obtained as a yellow mass, mp 78-80 °C (lit mp 78.7-79.2°C), 88%; ^{1}H NMR δ_H

7.45-7.32 (m, 3H), 7.20 (d, 2H, J = 7.4 Hz), 3.26 (s, 3H), 2.60-2.45 (m, 1H), 1.03 (d, 6H, J = 6.7 Hz); ^{13}C NMR δ_C 177.2, 144.1, 129.6, 127.5, 127.1, 37.3, 30.8, 19.5.

4.3.3 Reaction of *N*-(1-Butenyl)-*N*-methylaniline (**4.19**) With 1-Chloro-1*H*-1,2,3-benzotriazole (**4.14**)

To a 250 mL schlenk flask with magnetic stirrer and rubber septum was added enamine **4.19** (5 mmol, 0.81 g) under an argon atmosphere. Diethyl ether was added (100 mL), and the reaction vessel was placed in an acetonitrile/dry ice bath (-38 °C). After 30 min, a solution of 1-chloro-1*H*-1,2,3-benzotriazole (**4.14**, 5 mmol, 0.77 g) in diethyl ether (30 mL) was added dropwise. After 2 h at the same temperature, a solution of potassium *t*-butoxide (5.5 mmol, 0.61 g) in THF (30 mL) was added dropwise. After 30 min the bath was removed, and the reaction was stirred at rt for 4 h. Water (30 mL) was added, and the layers were separated. The aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic solutions were washed with brine, dried over anhydrous sodium sulfate, filtered, and condensed. The products were isolated by silica gel, flash column chromatography (10:1 pentane:ether).

N-[(*Z*)-1-(1*H*-1,2,3-Benzotriazol-1-yl)-1-butenyl]-*N*-methylaniline (**4.20a**). The title compound was obtained as a yellow oil, 35%; ^{1}H NMR δ_H 8.02 (d, 1H, J = 8.2 Hz), 7.52 (d, 1H, J = 8.2 Hz), 7.43 (t, 1H, J = 7.5 Hz), 7.33 (t, 1H, J = 7.5 Hz), 7.18 (t, 2H, J = 7.8 Hz), 7.07 (d, 2H, J = 8.0 Hz), 6.84 (t, 1H, J = 7.3 Hz), 5.52 (t, 1H, J = 7.6 Hz), 3.10 (s, 3H), 2.13-2.03 (m, 2H), 1.04 (t, 3H, J = 7.6 Hz); ^{13}C NMR δ_C 146.8, 145.4, 137.0, 132.7, 129.0, 127.9, 124.0, 121.0, 119.9, 119.2, 117.8, 110.8, 38.8, 20.5, 14.3. Anal.

Calcd for $C_{17}H_{18}N_4$: C, 73.35; H, 6.52; N, 20.13. Found: C, 73.15; H, 6.68; N, 20.02. Compound **4.20a** was also prepared from amide **4.16a** in 25% yield.

N-[(*E*)-1-(2*H*-1,2,3-Benzotriazol-2-yl)-1-butenyl]-*N*-methylaniline (**4.22b**). The title compound was obtained as yellow rods (ethyl acetate), mp 64-66 °C, 17%; ^{1}H NMR δ_H 7.82 (dd, 2H, *J* = 6.6, 3.0 Hz), 7.32 (dd, 2H, *J* = 6.6, 3.3 Hz), 7.19 (t, 2H, *J* = 7.8 Hz), 6.84 (d, 2H, *J* = 8.4 Hz), 6.77 (t, 1H, *J* = 7.3 Hz), 6.62 (t, 1H, *J* = 7.5 Hz), 3.32 (s, 3H), 2.33-2.23 (m, 2H), 1.13 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR δ_C 146.5, 144.4, 140.1, 129.1, 126.7, 125.0, 118.7, 118.3, 113.0, 38.4, 20.4, 13.3. Anal. Calcd for $C_{17}H_{18}N_4$: C, 73.35; H, 6.52; N, 20.13. Found: C, 73.14; H, 6.67; N, 20.07.

4.3.4 General Procedure for the Synthesis of *alpha*-Benzotriazolylenamines **4.20a-g**, **4.21a-f**, and **4.22a**

A pressure-equalized dropping funnel was placed on a 250 mL round bottom flask containing a magnetic stirrer, BtH (20 mmol, 2.38g), and a nitrogen inlet. Acetonitrile was added to the round bottom flask (10 mL) and to the dropping funnel (7 mL). The vessel was heated gently until the BtH dissolved, and then cooled to rt. Phosphorus oxychloride (10 mmol, 0.925 mL) was added to the dropping funnel, the contents of which were gently swirled and then added dropwise to the reaction vessel. The dropping funnel was rinsed with acetonitrile (7 mL) and then filled with the same. Triethylamine (10 mmol, 1.01 g) was added to the dropping funnel, the contents of which were swirled and then added dropwise to the vessel. After 15 min, a solution of amide **4.16** (5 mmol) in acetonitrile (3 mL) was added in one portion, and the dropping funnel replaced with a water-jacketed condenser topped with a nitrogen inlet. Complete reaction, as determined

by GC or TLC analysis, sometimes required refluxing. Volatile compounds were removed under reduced pressure using a rotary evaporator. The resulting oil was dissolved in chloroform (100 mL). Saturated aqueous potassium carbonate (200 mL) was added, and the mixture swirled. After 30 min the mixture was filtered through a medium sintered funnel under reduced pressure (water aspirator). The layers were separated, and the aqueous layer extracted with chloroform (50 mL). The combined organic solutions were dried over sodium sulfate, filtered, and had the solvent removed by rotary evaporation. The residue was purified by silica gel, flash column chromatography using a pentane/ether mixture as eluent.

N-[(*E*)-1-(1*H*-1,2,3-Benzotriazol-1-yl)-1-butenyl]-*N*-methylaniline (**4.21a**). Rt, 14 h, eluent 10:1, white prisms (ethyl acetate), mp 76-77 °C, 55%; ^{1}H NMR δ_H 8.02 (d, 1H, J = 8.0 Hz), 7.42-7.21 (m, 6H), 6.93 (d, 2H, J = 8.2 Hz), 6.82 (t, 1H, J = 7.1 Hz), 5.98 (t, 1H, J = 7.4 Hz), 3.11 (s, 3H), 2.20-2.09 (m, 2H), 1.09 (t, 3H, J = 7.5 Hz); ^{13}C NMR δ_C 145.8, 145.6, 135.6, 131.7, 129.2, 127.9, 123.9, 121.9, 119.8, 119.1, 113.6, 110.6, 36.8, 20.3, 13.2. Anal. Calcd for $C_{17}H_{18}N_4$: C, 73.35; H, 6.52; N, 20.13. Found: C, 73.13; H, 6.76; N, 20.33.

N-[(*Z*)-1-(1*H*-1,2,3-Benzotriazol-1-yl)-3,3-dimethylbut-1-enyl]-*N*-methylaniline (**4.20b**). Reflux, 10 d, eluent 6:1, yellow rods (ethyl acetate), mp 81-84 °C, 17%; ^{1}H NMR δ_H 8.02 (d, 1H, J = 8.2 Hz), 7.53 (d, 1H, J = 8.2 Hz), 7.43 (t, 1H, J = 7.5 Hz), 7.33 (t, 1H, J = 7.4 Hz), 7.23 (t, 2H, J = 8.1 Hz), 7.14 (d, 2H, J = 8.2 Hz), 6.86 (t, 1H, J = 7.2 Hz), 5.62 (s, 1H), 2.96 (s, 3H), 0.92 (s, 9H); ^{13}C NMR δ_C 147.1, 145.5, 134.6, 133.4, 130.5, 129.0, 128.0, 124.1, 120.6, 119.9, 117.5, 110.5, 37.9, 32.8, 30.1. Anal. Calcd for $C_{19}H_{22}N_4$: C, 74.48; H, 7.24; N, 18.28. Found: C, 74.78; H, 7.53; N, 18.68.

N-[(*E*)-1-(1*H*-1,2,3-Benzotriazol-1-yl)-3,3-dimethylbut-1-enyl]-*N*-methylaniline (**4.21b**). Reflux, 10 d, eluent 6:1, yellow oil, 36%; ^{1}H NMR δ_H 8.02 (d, 1H, J = 8.0 Hz), 7.47-7.28 (m, 3H), 7.20 (t, 2H, J = 7.7 Hz), 6.87 (d, 2H, J = 8.2 Hz), 6.78 (t, 1H, J = 7.1 Hz), 6.01 (s, 1H), 3.23 (s, 3H), 1.21 (s, 9H); ^{13}C NMR δ_C 146.6, 145.8, 133.8, 132.6, 132.2, 129.1, 127.9, 123.9, 120.0, 118.9, 113.6, 110.6, 39.1, 33.2, 29.5. Anal. Calcd for $C_{19}H_{22}N_4$: C, 74.48; H, 7.24; N, 18.28. Found: C, 74.58; H, 7.60; N, 18.67.

N-[(*Z*)-1-(1*H*-1,2,3-Benzotriazol-1-yl)-1-hexenyl]-*N*-methylaniline (**4.20c**). Rt, 14 h, eluent 8:1, yellow oil, 21%; ^{1}H NMR δ_H 8.02 (d, 1H, J = 8.2 Hz), 7.52 (d, 1H, J = 8.2 Hz), 7.43 (t, 1H, J = 7.5 Hz), 7.33 (t, 1H, J = 7.5 Hz), 7.18 (t, 2H, J = 7.6 Hz), 7.06 (d, 2H, J = 8.2 Hz), 6.84 (t, 1H, J = 7.2 Hz), 5.53 (t, 1H, J = 7.6 Hz), 3.10 (s, 3H), 2.07 (q, 2H, J = 7.3 Hz), 1.40-1.21 (m, 4H), 0.81 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ_C 146.8, 145.4, 137.3, 132.7, 129.0, 127.9, 124.0, 120.9, 119.9, 117.9, 117.8, 110.8, 38.8, 31.7, 26.7, 22.2, 13.8. Anal. Calcd for $C_{19}H_{22}N_4$: C, 74.48; H, 7.24; N, 18.28. Found: C, 74.19; H, 7.48; N, 18.60.

N-[(*E*)-1-(1*H*-1,2,3-Benzotriazol-1-yl)-1-hexenyl]-*N*-methylaniline (**4.21c**). Rt, 14 h, eluent 8:1, yellow oil, 58%; ^{1}H NMR δ_H 8.01 (d, 1H, J = 8.0 Hz), 7.42-7.20 (m, 5H), 6.92 (d, 2H, J = 7.8 Hz), 6.81 (t, 1H, J = 7.2 Hz), 5.99 (t, 1H, J = 7.3 Hz), 3.12 (s, 3H), 2.13 (q, 2H, J = 7.2 Hz), 1.56-1.30 (m, 4H), 0.88 (t, 3H, J = 6.9 Hz); ^{13}C NMR δ_C 145.7, 145.6, 135.9, 131.6, 129.1, 127.8, 123.8, 120.5, 119.7, 119.0, 113.5, 110.6, 36.8, 30.6, 26.4, 22.1, 13.6. Anal. Calcd for $C_{19}H_{22}N_4$: C, 74.48; H, 7.24; N, 18.28. Found: C, 74.29; H, 7.48; N, 18.61.

N-[(*Z*)-1-1*H*-1,2,3-Benzotriazol-1-yl)-1-hexenyl]-*N*-ethylaniline (**4.20d**). Rt, 14 h, eluent 10:1, yellow oil, 31%; ^{1}H NMR δ_H 8.02 (d, 1H, J = 8.2 Hz), 7.55 (d, 1H, J = 8.2

Hz), 7.42 (t, 1H, J = 7.3 Hz), 7.33 (t, 1H, J = 7.5 Hz), 7.21-7.08 (m, 4H), 6.83 (t, 1H, J = 7.2 Hz), 5.56 (t, 1H, J =7.6 Hz), 3.44 (q, 2H, J = 7.1 Hz), 2.09-2.02 (m, 2H), 1.44-1.34 (m, 2H), 1.33-1.16 (m, 5H), 0.81 (t, 3H, J = 7.3 Hz); ^{13}C NMR δ_C 145.7, 145.4, 136.0, 132.7, 129.1, 127.8, 124.0, 120.7, 119.8, 118.5, 118.2, 110.8, 44.5, 31.7, 26.8, 22.2, 13.7, 12.4. Anal. Calcd for $C_{20}H_{24}N_4$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.76; H, 7.82; N, 17.87.

N-[(*E*)-1-(1*H*-1,2,3-Benzotriazol-1-yl)-1-hexenyl]-*N*-ethylaniline (**4.21d**). Rt, 14 h, eluent 10:1, yellow oil, 53%; ^{1}H NMR δ_H 8.06 (dd, 1H, J = 7.0, 1.9 Hz), 7.45-7.26 (m, 5H), 7.03 (d, 2H, J = 8.0 Hz), 6.86 (t, 1H, J = 7.3 Hz), 6.01 (t, 1H, J = 7.3 Hz), 3.33 (q, 2H, J = 7.1 Hz), 2.07 (q, 2H, J = 7.3 Hz), 1.50-1.31 (m, 4H), 1.21 (t, 3H, J = 7.0 Hz), 0.87 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ_C 145.9, 145.4, 134.4, 131.9, 129.4, 127.9, 124.0, 121.9, 119.9, 119.0, 114.1, 111.1, 42.7, 30.6, 26.9, 22.4, 13.8, 12.6. Anal. Calcd for $C_{20}H_{24}N_4$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.91; H, 7.22; N, 17.72.

N-[(*Z*)-1-(1*H*-1,2,3-Benzotriazol-1-yl)-1-hexenyl]-*N*-phenylaniline (**4.20e**). Reflux, 3 d, eluent 6:1, yellow oil, 18%; ^{1}H NMR δ_H 7.95 (d, 1H, J = 8.2 Hz), 7.77 (d, 1H, J = 8.2 Hz), 7.44 (t, 1H, J = 7.6 Hz), 7.28 (t, 1H, J = 8.2 Hz), 7.22-7.14 (m, 9H), 6.96-6.91 (m, 2H), 5.57 (t, 1H, J = 7.7 Hz), 2.15 (q, 2H, J = 7.4 Hz), 1.42-1.19 (m, 4H), 0.80 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ_C 145.2, 136.4, 132.5, 129.1, 127.9, 124.0, 123.3, 122.9, 120.6, 119.9, 110.7, 31.4, 26.9, 22.2, 13.7. Anal. Calcd for $C_{24}H_{24}N_4$: C, 78.23; H, 6.56; N, 15.20. Found: C, 77.96; H, 6.89; N, 15.37.

N-[(*E*)-1-(1*H*-1,2,3-Benzotriazol-1-yl)-1-hexenyl]-*N*-phenylaniline (**4.21e**). Reflux, 3 d, eluent 6:1, white rods (ethyl acetate), mp 94-96 °C, 53%; ^{1}H NMR δ_H 7.92 (d, 1H, J = 8.2 Hz), 7.74 (d, 1H, J = 8.5 Hz), 7.37 (t, 1H, J = 7.6 Hz), 7.28-7.17 (m, 9H), 6.94 (t,

2H, J = 7.0 Hz), 5.94 (t, 1H, J = 7.4 Hz), 2.05 (q, 2H, J = 7.2 Hz), 1.43-1.23 (m, 4H), 0.82 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ_C 145.7, 143.9, 134.9, 131.8, 129.2, 127.8, 123.9, 123.0, 121.3, 120.4, 119.8, 110.8, 30.4, 26.4, 22.3, 13.7. Anal. Calcd for $C_{24}H_{24}N_4$: C, 78.23; H, 6.56; N, 15.20. Found: C, 77.91; H, 6.59; N, 15.39.

N-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2-phenylethenyl]-*N*-methylaniline (**4.20f** and **4.21f**). Reflux, 3 d, eluent 6:1, viscous yellow oil, 56%; signals given for major isomer only ^{1}H NMR δ_H 8.04 (d, 1H, J = 8.2 Hz), 7.49 (d, 1H, J = 8.2 Hz), 7.44-7.11 (m, 9H), 6.92 (d, 2H, J = 8.2 Hz), 6.80-6.76 (m, 2H), 3.30 (s, 3H); ^{13}C NMR δ_C 146.0, 144.5, 136.0, 133.6, 132.1, 129.3, 128.6, 128.2, 128.0, 127.3, 124.3, 120.3, 120.2, 116.9, 114.9, 110.8, 38.1. Anal. Calcd for $C_{21}H_{18}N_4$: N, 17.17. Found: N, 17.31.

N-[1-(1*H*-1,2,3-Benzotriazol-1-yl)-2-methyl-1-propenyl]-*N*-methylaniline (**4.20g**). Reflux, 2 d, eluent 4:1, colorless rhomboids (ethyl acetate), mp 106-107 °C, 74%; ^{1}H NMR δ_H 8.05 (d, 1H, J = 7.8 Hz), 7.40-7.24 (m, 5H), 6.92 (d, 2H, J = 8.2 Hz), 6.82 (t, 1H, J = 7.2 Hz), 3.01 (s, 3H), 1.85 (s, 3H), 1.72 (s, 3H); ^{13}C NMR δ_C 146.3, 145.3, 133.0, 130.4, 129.3, 129.2, 127.9, 123.9, 119.9, 118.6, 113.3, 110.6, 36.3, 19.9, 19.7. Anal. Calcd for $C_{17}H_{18}N_4$: C, 73.35; H, 6.52; N, 20.13. Found: C, 73.40; H, 6.74; N, 20.29.

N-[1-(2*H*-1,2,3-Benzotriazol-2-yl)-2-methyl-1-propenyl]-*N*-methylaniline (**4.22a**). Reflux, 2 d, eluent 4:1, yellow oil, 1%; ^{1}H NMR δ_H 7.86 (dd, 2H, J = 6.5, 3.0 Hz), 7.35 (dd, 2H, J = 6.6, 3.0 Hz), 7.25-7.19 (m, 2H), 6.92 (d, 2H, J = 8.2 Hz), 6.76 (t, 1H, J = 7.2 Hz), 3.20 (s, 3H), 1.90 (s, 3H), 1.81 (s, 3H); ^{13}C NMR δ_C 146.5, 143.9, 135.6, 131.1, 129.1, 126.6, 118.5, 118.4, 113.3, 37.6, 19.8, 19.5. Anal. Calcd for $C_{17}H_{18}N_4$: C, 73.35; H, 6.52; N, 20.13. Found: C, 73.57; H, 6.70; N, 20.29.

1-(1*H*-1,2,3-Benzotriazol-1-yl)butan-1-one (**4.24**) [96MI881]. The title compound was prepared using the general procedure for the synthesis of *alpha*-benzotriazolylenamines, except that1-(trimethylsilyl)-1*H*-1,2,3-benzotriazole (**4.23**) was used instead of BtH in the reaction with the amide *N*-methyl-*N*-phenylbutanamide (**4.16a**). Rt, 14 h, eluent 10:1, white rods (ethyl acetate), mp 56-57 °C (lit mp 54-55 °C), 46%; ^{1}H NMR δ_H 8.29 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 3.42 (t, J = 7.3 Hz, 2H), 2.04-1.87 (m, 2H), 1.12 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ_C 172.5, 146.1, 131.1, 130.3, 126.0, 120.1, 114.4, 37.3, 17.9, 13.7.

N-Methyl-*N*-[2-methyl-1-(2-phenylethynyl)-1-propenyl]aniline (**4.26**). To a solution of *N*-[1-(2*H*-1,2,3-benzotriazol-2-yl)-2-methyl-1-propenyl]-*N*-methylaniline (**4.22a**) (4 mmol) in toluene (40 mL) under a nitrogen atmosphere was added a solution made from phenylethynylmagnesium bromide (4.4 mL, 1.0 M in THF) and $ZnCl_2$ (4.4 mL, 1.0 M in Et_2O). The mixture was heated to 60 °C for 20 h. The reaction was quenched with an aqueous, saturated K_2CO_3 solution (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, and had the volatiles removed by rotary evaporation. The title compound was obtained in 76% yield as a red oil by silica gel, flash column chromatography using pentane as eluent; ^{1}H NMR δ_H 7.33-7.15 (m, 7H), 6.75-6.71 (m, 3H), 3.01 (s, 3H), 2.07 (s, 3H), 1.73 (s, 3H); ^{13}C NMR δ_C 147.9, 141.4, 131.3, 128.8, 128.0, 127.7, 123.3, 122.6, 117.2, 113.0, 90.7, 86.0, 37.2, 21.4, 18.9. Anal. Calcd for $C_{19}H_{19}N$: N, 5.36. Found: N, 5.27.

CHAPTER 5
SYNTHESIS AND UTILITY OF 1-BENZOTRIAZOLYL-3-PHENYLSULFONYLPROP-1-ENE

5.1 Introduction

Sulfonyl [93MI1] and benzotriazolyl [98CRV409] groups are among the most useful synthetic auxiliaries, and their chemistries have been extensively studied. One characteristic of a good synthetic auxiliary is its ability to exert an activating affect on the molecule. In allylic systems, both sulfonyl [93MI116, 77JCS(P1)123, 83JOC910, 85JA396] and benzotriazolyl [99JPR79, 92LA843] groups behave as strong *alpha*-alkylation directors (Figure 5.1). When other groups, such as alkylthio [84TL2671], alkoxy [92TL7445], acyl [80JA1602], alkoxycarbonyl [80JA1602, 73BSF743, 96T15243], and carbamoyl [96TL4787], are present on the *gamma*-position of an allylic sulfone, products **5.2** resulting from *alpha*-alkylation (to the sulfone) of the ambident anion usually predominate. However, sometimes *gamma*-alkylation products **5.3** are isolated when an acyl [80JA1602] or alkoxycarbonyl [73BSF743, 96T15243] group is at the *gamma*-position of an allylic sulfone; this phenomenon is believed to be due to steric effects. When an alkoxy [95S1315] or amino [95TL343] group is present at the *gamma*-position of a 1-allylbenzotriazole, only products with alkylation *alpha* to Bt **5.3** are obtained. Since both the sulfonyl and benzotriazolyl groups are highly useful in organic synthesis, this investigation was undertaken in order to test and compare the effect of a

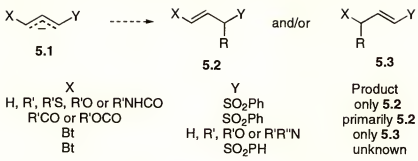


Figure 5.1. Alkylation of Allylic Anions

benzotriazolyl group together with a phenylsulfonyl group on the alkylation of an allylic anion **5.1**.

5.2 Results and Discussion

5.2.1 Synthesis of (*E*)-1-Benzotriazolyl-3-(phenylsulfonyl)-1-propene (**5.6**)

A synthetic pathway to the desired precursor of the allylic anion **5.1** (X = Bt, Y = $PhSO_2$) was devised through the use of established literature methods. First, allyl phenyl sulfone (**5.4**) was produced in 95% yield by refluxing allyl bromide and the sodium salt of benzenesulfinic acid for 26 h in methanol, followed by work-up as described in the experimental section (Figure 5.2) [79JOC3277]. The identity of compound **5.4** was verified by comparison of its NMR data with that found in the literature.

Using the literature procedure [79JOC3277], compound **5.4** was then brominated/ dehydrobrominated in one pot (Figure 5.3); however, the intermediate dibromo derivative of compound **5.4** was not isolated as was done in the literature procedure. This reaction gave an E:Z mixture (76:24) of 3-bromo-1-propenyl phenyl sulfone (**5.5**) in 88% yield, as

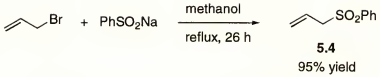


Figure 5.2. Synthesis of Allyl Phenyl Sulfone

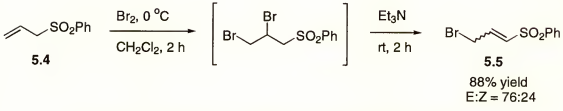


Figure 5.3. Synthesis of 3-Bromo-1-propenyl Phenyl Sulfone

compared with the 75:25 mixture of compound **5.5** in 80% yield obtained by Eisch and Galle. The identity of compound **5.5** was verified by comparison of its NMR spectral data with that found in the literature.

Purification of compound **5.5** was not necessary for successful preparation of (*E*)-1-benzotriazolyl-3-(phenylsulfonyl)-1-propene (**5.6**) in the next step. When crude 3-bromo-1-propenyl phenyl sulfone (**5.5**) was reacted with a mixture of BtH and potassium hydroxide in dimethyl sulfoxide at rt for 1 d, a Bt^1/Bt^2 mixture of (*E*)-1-benzotriazolyl-3-(phenylsulfonyl)-1-propene (**5.6a**:**5.6b** = 2:1) was obtained in 78% yield after work-up and column chromatography (Figure 5.4). No isomer **5.7**, with the double bond *alpha*, *beta* to the sulfonyl group, was detected. The E stereochemistry was assigned to compounds **5.6a,b** since the C2 proton [6.42 (dt, 1H, J = 7.7, 14.3 Hz) and 6.83 (dt, 1H, J = 8.2, 14.0 Hz), respectively] of each gave such a large 14 Hz coupling constant, which is typical of protons being trans to each other across a double bond. The structures of

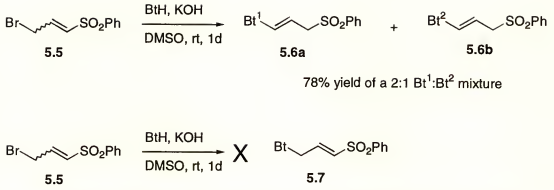


Figure 5.4. Synthesis of (*E*)-1-Benzotriazolyl-3-(phenylsulfonyl)-1-propene

compounds **5.6a**,**b** were determined by comparing their ^{1}H and ^{13}C NMR spectra with those of 1-allylbenzotriazole (**5.8**) and allyl phenyl sulfone (**5.4**, Figure 5.5, Table 5.1). The NMR chemical shifts of the methylene unit of **5.6a**,**b** (δ_H 4.08 and 4.06, δ_C 57.4 and 57.2) are similar to those of the methylene unit of allyl phenyl sulfone (**5.4**, δ_H 3.84, δ_C 60.6), but not to those of 1-allylbenzotriazole (**5.8**, δ_H 5.27 and 5.34, δ_C 50.6 and 58.7).

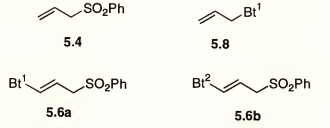


Figure 5.5. Structures of Selected Allylic Compounds

Table 5.1. Comparison of Selected NMR Data for Identification of Intermediates **5.6a**,**b**

Compound	Methylene signal δ_H (ppm)	Methylene signal δ_C (ppm)
5.4	3.84	60.6
5.8	5.27	50.6
5.6a	4.08	57.4
5.6b	4.06	57.2

The production of compounds **5.6a**,**b** to the exclusion of compound **5.7** under basic conditions for an extended period (24 h) indicates that compounds **5.6a**,**b** are more stable than compound **5.7**. Additionally, attempts to isomerize the double bond of compound **5.6a** (**5.6a** to **5.7**) failed. When compound **5.6a** was treated with 1.0 equiv of potassium *tertiary*-butoxide in THF at rt for 24 h (Figure 5.6), the addition product **5.9** was obtained quantitatively (^{1}H NMR). When 0.1 equiv of potassium *tertiary*-butoxide was used only a small portion of compound **5.6a** was converted, and most of that was to compound **5.9**. These results are not unexpected if one considers that (1) allyl sulfones are more thermodynamically stable than the corresponding vinyl isomers [93MI39] and (2) 1-propenylbenzotriazoles can be isomerized into the corresponding 2-propenylbenzotriazoles [92LA843, 69JCS(C)1478]. Compound **5.9** gave satisfactory elemental analysis (± 0.4%) as well as both ^{1}H and ^{13}C NMR spectra consistent with the proposed structure.

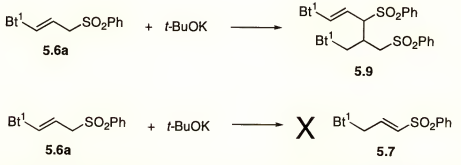


Figure 5.6. Attempted Isomerization of (*E*)-1-Benzotriazol-1-yl-3-(phenylsulfonyl)-1-propene

5.2.2 Alkylation of (*E*)-1-Benzotriazolyl-3-(phenylsulfonyl)-1-propene (**5.6**)

The reaction of compound **5.6a** with 1.0 equiv of lithium diisopropylamide followed by 1.0 equiv of benzyl bromide gave only products arising from alkylation *alpha* to the sulfonyl moiety (Figure 5.7, Table 5.2), in addition to 16% unreacted starting material. It was also shown that if only the Bt^1 compound **5.6a** was used as starting material in this reaction, only Bt^1 products **5.10a** and **5.11a** were isolated. Similarly, Bt^2 compound **5.6b** only gave the Bt^2 products **5.12a** and **5.13a**. This similar reactivity of the two isomers allowed the use of the mixture **5.6a,b** in further reactions. The use of methyl iodide as electrophile also gave solely products of *alpha*-alkylation to the phenylsulfonyl group, with the ratio, based on ^{1}H NMR of the crude product, of di- **5.11b** to mono- **5.10b** alkylation products being 1.33:1 rather than 1:3.45 with benzyl bromide. When butyl bromide was used as the electrophile, the same *alpha*-regioselectivity was observed; a ratio (1.44:1) of dialkylated **5.11c** to monoalkylated **5.10c** products similar to that found for methyl iodide was observed. In addition to alkylation products **5.10c** and **5.11c**, reaction of compound **5.6a** with butyl iodide also afforded addition product **5.9** in 32% isolated yield.

Compounds **5.10a,c**, **5.11a,c**, and **5.12a** each satisfactorily gave either elemental analysis or HRMS. As indicated earlier, the methylene unit of allyl phenyl sulfone (**5.4**) exhibits its ^{1}H NMR signal much further upfield (δ_H = 3.84 ppm) than that of 1-allylbenzotriazole (**5.8**, δ_H = 5.27), but a more shielded ^{13}C NMR signal (δ_C = 60.6 versus 50.6 ppm) [92LA843]. Since 1-(1-butyl-2-propenyl)benzotriazole (**5.14c**) and 1-(1-benzyl-2-propenyl)benzotriazole (**5.14a**) give ^{1}H NMR signals at δ_H = 5.33-5.36 and 5.50-5.54 ppm, respectively, while the monobutyl **5.10c** and monobenzyl **5.10a** products

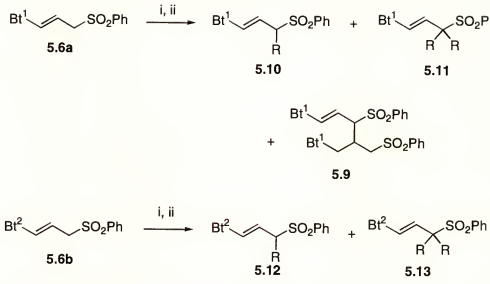


Figure 5.7. Reaction of (*E*)-1-Benzotriazolyl-3-(phenylsulfonyl)-1-propene With One Equivalent of LDA and Alkyl Halide

Table 5.2. Isolated Compounds from Reaction of Compound **5.6** With LDA (1.0 equiv) and Alkyl Halide (1.0 equiv)

			Products [a]		
5.6	Recovered **5.6** (%)	RX	**5.10/5.12** (% Yield)	**511/5.13** (% Yield)	**5.9** Yield (%)
a	16	$PHCH_2Br$	**5.10a** (38)	**5.11a** (6)	0
b	22	$PHCH_2Br$	**5.12a** (38)	**5.13a** (0)	0
a	34	MeI	**5.10b** ([b])	**5.11b** ([b])	0
a	12	BuBr	**5.10c/5.12c** (18)	**5.11c/5.13c** (26)	32

[a]: Yield of products based upon equiv of consumed compound **5.6**. [b]: A 2:3 mixture of compounds **5.10b** and **5.11b** was isolated in 75% yield.

from these reactions gave ^1H NMR signals at δ_H = 3.76 and 3.03 ppm, respectively (Figure 5.8, Table 5.3), the position of alkylation was assigned to be *alpha* to the sulfonyl group; the Bt^2-monobenzyl compound **5.12a** also gave an upfield signal (δ_H = 3.98 ppm). Similarly, the ^{13}C NMR spectra of the dibenzyl **5.11a** (δ_C = 70.6 ppm), dimethyl **5.11b** (δ_C = 63.6 ppm), and dibutyl **5.11c** (δ_C = 69.8 ppm) products were more shielded than the

corresponding 1-(1-benzyl-2-propenyl)benzotriazole (**5.14a**, δ_C = 65.3 ppm), 1-(1-methyl-2-propenyl)benzotriazole (**5.14b**, δ_C = 57.5 ppm), and 1-(1-butyl-2-propenyl)benzotriazole (**5.14c**, δ_C = 62.3 ppm) [92LA843].

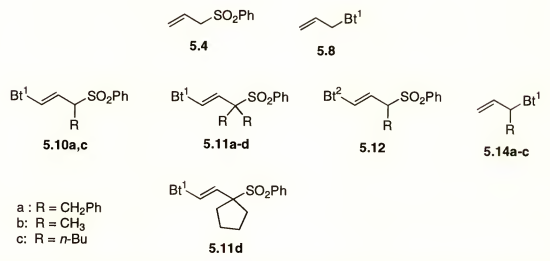


Figure 5.8. Compounds Utilized in Determining the Structures for Compounds **5.10**-**5.12**

Table 5.3. Comparison of Selected NMR Data for Identification of Compounds **5.10a,c**, **5.11a-d**, and **5.12**

Compound	Methylene signal δ_H (ppm)	Methylene signal δ_C (ppm)
5.4	3.84	60.6
5.8	5.27	50.6
5.10a	3.76	68.7
5.10c	3.03	67.5
5.11a	-	70.6
5.11b	-	63.6
5.11c	-	69.8
5.11d	-	73.6
5.12	3.98	68.4
5.14a	5.50-5.54	65.3
5.14b	5.57	57.5
5.14c	5.33-5.36	62.3

Since it has been reported that the use of 2.0 equiv of base is sometimes necessary for alkylation of similar allylic systems to occur [96CRV3241, 85AGE610], and since these conditions usually give high yields of dialkylated products, such conditions were tested on this system. When (*E*)-1-benzotriazolyl-3-(phenylsulfonyl)-1-propene (**5.6**) was treated with 2.1 equiv of LDA at –78 °C and then 2.0 equiv of alkyl halide, high yields of product dialkylated *alpha* to the sulfone were obtained (Figure 5.9). Reaction of compound **5.6a** with benzyl bromide gave dialkylated product **5.11a** in 82% yield, while methyl iodide and mixture **5.6a,b** gave mixture **5.11b**, **5.13b** in 84% yield. It was also shown that the dianion generated from compound **5.6** can also react with *alpha*, *omega*-dibromoalkanes to form the cyclized product. For example, the preformed dianion, from

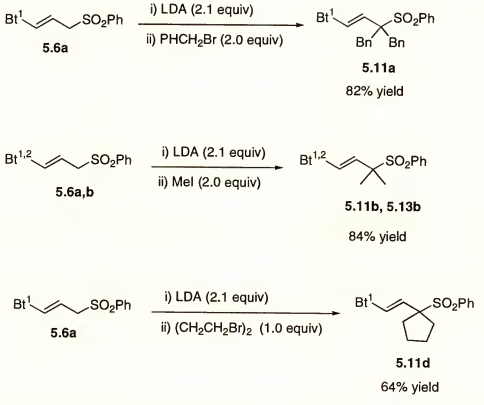


Figure 5.9. Dialkylation of (*E*)-1-Benzotriazolyl-3-(phenylsulfonyl)-1-propene

compound **5.6a**, reacted with 1,4-dibromobutane to give product **5.11d** in 64% yield. In addition to giving satisfactory elemental analysis, compound **5.11d** gave NMR spectra consistent with the structure. Moreover, this cyclic product's ^{13}C NMR signal for the site of alkylation was more deshielded than that of the other dialkylated products (δ_C = 73.6 ppm versus δ_C = 63.6 ppm for the dimethyl analog **5.11b**), and therefore was assigned to be *alpha* to the sulfonyl group.

One further experiment was performed in which compound **5.6a** was treated with 1.0 equiv of LDA followed by butyl bromide at –78 °C and the temperature raised slowly (Table 5.4). The reaction was followed by TLC as the temperature was increased. Two h after the addition of electrophile, and having been kept at –78 °C, no reaction had occurred. The temperature was then raised to –42 °C (acetonitrile-dry ice bath), and, after an additional 2 h, there was still no reaction. After 2 h at –15 °C (ethylene glycol-dry ice bath), small quantities of compounds **5.11c** and **5.9** were produced. Two h at 0 °C only resulted in an increase in the quantities of products detected. The reaction temperature was then raised to rt, and the mixture was allowed to stir for 24 h. The reaction went to completion and formed mostly compound **5.11c** and addition product **5.9**, but a small quantity of compound **5.10c** was also produced. The formation of the dialkylated

Table 5.4. Relative Product Distribution at Various Temperatures in the Reaction of Compound **5.6a** with LDA (1.0 equiv) and Butyl Bromide (1.0 equiv)

Temp. (°C)	Time (h)	**5.6a**	**5.10c**	**5.11c**	**5.9**
-78	2	all	none	none	none
-42	2	all	none	none	none
-15	2	substantial	none	little	little
0	2	substantial	none	substantial	substantial
20	24	none	little	substantial	substantial

compound **5.11c** prior to the monoalkylated product **5.10c** indicates that some of the anion of compound **5.10** is generated even when only 1.0 equiv of base is utilized.

5.2.3 Use of Bases Other Than LDA

After a successful method for reacting compound **5.6** with alkyl halides had been developed, bases other than LDA were tested (Figure 5.10). Since reacting compound **5.6b** and benzyl bromide gave the fewest number of products when LDA was utilized, this system was used to test the applicability of sodium hydride and sodium methoxide as base. When solid NaH (2 equiv) was added at –40 °C to a THF solution of compound **5.6b**, a blood red solution, typical of the anion of compound **5.6**, was produced. However, subsequent treatment with benzyl bromide and slow warming to rt resulted in a complex product slate, that by GC/MS of the crude reaction mixture, contained neither starting material nor desired products. The reaction using $NaOCH_3$ instead of NaH produced similar results. Thus, it appeared that the use of LDA as base was essential for successful alkylation, but not for formation of the anion.

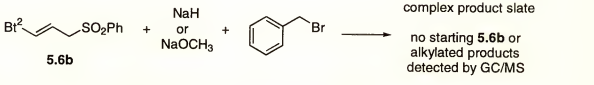
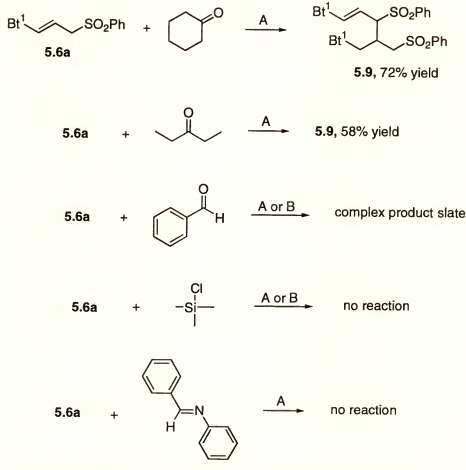


Figure 5.10. Attempted Alkylation of (*E*)-1-Benzotriazolyl-3-(phenylsulfonyl)-1-propene With Bases Other Than LDA

5.2.4 Reaction of (*E*)-1-Benzotriazolyl-3-(phenylsulfonyl)-1-propene (**5.6**) With Other Electrophiles

After optimization of experimental conditions for the reaction of compound **5.6** with alkyl halides, the reactivity of the anion of compound **5.6** toward other electrophiles was studied(Figure 5.11). Thus, (*E*)-1-(benzotriazol-1-yl)-3-(phenylsulfonyl)-1-propene (**5.6a**) was treated with LDA (1.1 equiv) at –78 °C for 0.5 h and then with electrophile (1.0 equiv), before the temperature was slowly raised to rt over 18 h. When



A: i) LDA (1.1 equiv), THF, -78 °C, 0.5 h; ii) RX, -78 °C -> rt, 18 h
B: i) LDA (2.2 equiv), THF, -78 °C, 0.5 h; ii) RX, -78 °C -> rt, 18 h

Figure 5.11. Reaction of (*E*)-1-Benzotriazol-1-yl-3-(phenylsulfonyl)-1-propene With Electrophiles Other Than Alkyl Halides

cyclohexanone was used as the electrophile, a 72% yield of addition product **5.9** was isolated as the sole product. Similarly, 3-pentanone gave compound **5.9** in 58% yield, as the only isolated product. The use of benzaldehyde as electrophile produced a complex product slate containing neither desired products, starting material, nor addition product **5.9**, as determined by GC/MS. Starting material was recovered when chlorotrimethylsilane or the imine PhCH=NPh was used as the electrophile. When the amount of LDA used was doubled, chlorotrimethylsilane was still unreactive and the benzaldehyde reaction again gave a complex product slate. Thus, the anion of compound **5.6** shows variable reactivity toward electrophiles, and is only preparatively useful in reaction with alkyl halides.

In summary, (*E*)-1-benzotriazolyl-3-(phenylsulfonyl)-1-propene (**5.6**) was easily prepared from allyl bromide in a three step sequence in 74% overall yield. A temperature study showed that products formally derived from the dianion of (*E*)-1-benzotriazolyl-3-(phenylsulfonyl)-1-propene are formed even when only 1.0 equiv of LDA is utilized. It was also shown that the use of 2.1 equiv of LDA and electrophile gave high yields of *alpha*, *alpha*-dialkylated products. The easy generation of the first carbanion and that of the carbanion of the monoalkylated compound, as well as the regioselectivity in the alkylation of compound **5.6**, can be attributed to the greater capability of a sulfonyl group to stabilize an adjacent carbanion as compared to that of a benzotriazolyl group. However, the low reactivity of the anions toward electrophiles other than alkyl halides limits the application of this method.

5.3 Experimental

5.3.1 General Comments

All melting points were measured on a hot-stage microscope and are uncorrected. NMR experiments were conducted with a Varian VXR-300 NMR spectrometer at 75 MHz for ^{13}C and 300 MHz for ^{1}H spectra. Samples were dissolved in deuteriochloroform with the internal reference being TMS (δ_H = 0.00 ppm) for ^{1}H spectra and solvent (δ_C = 77.0 ppm) for ^{13}C spectra. Elemental analyses were performed on a Carlo Erba-1106 elemental analyzer. High resolution mass measurements were recorded on an AEI MS-30 mass spectrometer. Column chromatography was carried out using 230-400 mesh silica gel. Immediately prior to use, THF and diethyl ether were distilled from sodium/ benzophenone. Methylene chloride was dried over 4Å molecular sieves. All other chemicals were obtained from commercial sources and were not further purified. Reactions were carried out under dry nitrogen with magnetic stirring. Molecular sieves were activated by microwave irradiation.

Allyl phenyl sulphone (**5.4**) and 3-bromo-1-propenyl phenyl sulphone (**5.5**) were prepared by literature methods [79JOC3277].

Allyl phenyl sulfone (**5.4**). A mixture of allyl bromide (0.30 mol) and the sodium salt of benzenesulfinic acid (0.4 mol) was refluxed for 26 h in methanol. After cooling, the volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 33 mL). The combined organics were dried over anhydrous sodium sulfate and filtered. Removal of solvent gave the title compound **5.4** in 95% yield as a yellow oil; ^{1}H

NMR δ_H 7.90-7.87(m, 2H), 7.70-7.64 (m, 1H), 7.60-7.54 (m, 2H), 5.86-5.73 (m, 1H), 5.34 (d, 1H, J = 11.2 Hz), 5.17 (d, 1H, J = 17.0 Hz), 3.84 (d, 2H, J = 7.4 Hz); ^{13}C NMR δ_C 138.1, 133.6, 128.9, 128.3, 124.5, 124.4, 60.6.

3-Bromo-1-propenyl phenyl sulfone (**5.5**). To a solution of allyl phenyl sulfone (**5.4**, 0.10 mol in 50 mL of CH_2Cl_2) in an ice-water bath was added dropwise a solution of bromine (0.10 mol in 50 mL of CH_2Cl_2). After 1.5 h, triethylamine (0.105 mmol) was added dropwise, and the mixture was then stirred for 2 h. The volatiles were removed from the crude product under reduced pressure. The residue was treated with $HCl_{(aq)}$ (1N, 100 mL) and extracted with diethyl ether (2 x 100 mL). The combined organics were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give an 88% yield of the title compound **5.5** as a 76:24 E:Z mixture. Yellow oil; ^{1}H NMR (minor isomer in square brackets) δ_H 7.95-7.82 (m, 2H), 7.70-7.50 (m, 3H), 7.08-6.95 (m, 1H) [6.50-6.38 (m, 1H)], 6.56 (d, 1H, J = 14.1 Hz) [6.48-6.18 (m, 1H)], 4.02 (d, 2H, J = 7.5 Hz) [4.04 (d, 2H, J = 7.6 Hz)].

(*E*)-1-(Benzotriazol-1-yl)-3-(phenylsulfonyl)-1-propene (**5.6a**) and (*E*)-1-(benzotriazol-2-yl)-3-(phenylsulfonyl)-1-propene (**5.6b**). A mixture of BtH (6.3 mmol), 3-bromo-1-propenyl phenyl sulfone (**5.5**, 6.0 mmol) and potassium hydroxide (6.5 mmol) were stirred in dimethyl sulfoxide (15 mL) at rt for 1 d. The reaction was quenched with $HCl_{(aq)}$ (1N, 10 mL) and extracted with ethyl acetate (20 mL). The organics were washed with $HCl_{(aq)}$ (0.5N, 3 x 5 mL) and then with water (5 mL). The aqueous solution was extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with brine (5 mL), dried over anhydrous sodium sulfate, and evaporated to give an oil. The products

(**5.6a**:**5.6b** = 2:1) were isolated independently by column chromatography in 78% total yield using methylene chloride as eluent.

(*E*)-1-(Benzotriazol-1-yl)-3-(phenylsulfonyl)-1-propene (**5.6a**). The title compound was obtained as a white solid (ethyl acetate), mp 157-158 °C; ^{1}H NMR δ_H 8.09 (d, 1H, *J* = 8.3 Hz), 7.96-7.93 (m, 2H), 7.71-7.55 (m, 5H), 7.47-7.38 (m, 2H), 6.42 (dt, 1H, *J* = 7.7, 14.3 Hz), 4.08 (dd, 2H, *J* = 0.9, 8.0 Hz); ^{13}C NMR δ_C 146.0, 133.9, 132.2, 130.8, 129.4, 129.0, 128.4, 128.2, 124.5, 120.2, 109.5, 106.2, 57.4. Anal. Calcd for $C_{15}H_{13}N_3O_2S$: C, 60.19; H, 4.38; N, 14.04. Found: C, 60.36; H, 4.36; N, 13.55.

(*E*)-1-(Benzotriazol-2-yl)-3-(phenylsulfonyl)-1-propene (**5.6b**). The title compound was obtained as a white solid (ethyl acetate), mp 168-169 °C; ^{1}H NMR δ_H 7.93 (d, 2H, *J* = 7.7 Hz), 7.84-7.81 (m, 2H), 7.66 (t, 1H, *J* = 7.6 Hz), 7.56 (t, 2H, *J* = 7.6 Hz), 7.42-7.35 (m, 3H), 6.83 (dt, 1H, *J* = 8.2, 14.0 Hz), 4.06 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR δ_C 144.8, 137.6, 134.5, 134.1, 129.3, 128.4, 127.7, 118.2, 111.0, 57.2. Anal. Calcd for $C_{15}H_{13}N_3O_2S$: C, 60.19; H, 4.38; N, 14.04. Found: C, 60.46; H, 4.37; N, 13.85.

5.3.2 General Procedure for the Alkylation of (*E*)-1-Benzotriazolyl-3-(phenylsulfonyl)-1-propene (**5.6**)

Method A. To a solution of compound **5.6** (1 or 2 mmol) in tetrahydrofuran (20 mL) at –78 °C was added 1.05 equiv of lithium diisopropylamide (1.5M in cyclohexane) under an inert atmosphere. After 30 min of stirring, 1.0 equiv of electrophile was added, and the solution allowed to warm to rt overnight. The reaction was quenched by water (10 mL) and the layers separated. The aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organics were washed with brine (5 mL), dried over anhydrous

sodium sulfate, and evaporated to give a residue, which was then purified by column chromatography.

Method B. The same as Method A, except that 2.1 equiv of lithium diisopropylamide and 2.0 equiv of electrophile were used instead.

(*E*)-1,5-Di(benzotriazol-1-yl)-3-(phenylsulfonyl)-4-[(phenylsulfonyl)methyl]-1-pentene (**5.9**). The title compound was obtained as a white solid (ethyl acetate) from the reaction of compound **5.6a** with *n*-butyl bromide by Method A (32% yield), with cyclohexanone by Method A (72% yield), and without electrophile by Method B using potassium *tertiary*-butoxide as base instead of lithium diisopropylamide (quantitative by ^{1}H NMR), mp 129-132 °C; ^{1}H NMR δ_H 8.12-8.03 (m, 4H), 7.78-7.58 (m, 7H), 7.53-7.33 (m, 6H), 7.26-7.19 (m, 2H), 6.49 (dd, 1H, *J* = 11.0, 14.0 Hz), 5.39 (dd, 1H, *J* = 2.5, 14.8 Hz), 4.85-4.77 (m, 1H), 4.28 (d, 1H, *J* = 12.4 Hz), 3.94 (d, 1H, *J* = 10.7 Hz), 3.32-3.28 (m, 2H); ^{13}C NMR δ_C 146.1, 145.9, 138.8, 136.0, 134.5, 134.1, 132.7, 131.6, 131.5, 129.7, 129.1, 129.0, 128.4, 128.2, 125.1, 124.5, 120.5, 120.0, 109.6, 109.5, 105.1, 64.9, 53.3, 47.9, 34.0. Anal. Calcd for $C_{30}H_{26}N_6O_4S_2$: C, 60.19; H, 4.38; N, 14.04. Found: C, 60.33; H, 4.41; N, 13.72.

(*E*)-1-(Benzotriazol-1-yl)-3-phenylsulfonyl-4-phenyl-1-butene (**5.10a**). The title compound was obtained from the reaction of compound **5.6a** with benzyl bromide by Method A as a white solid (ethyl acetate) in 38% yield, mp 187-189 °C; ^{1}H NMR δ_H 8.04 (d, 1H, *J* = 8.2Hz), 7.95 (d, 2H, *J* = 7.6 Hz), 7.65 (t, 1H, *J* = 7.4 Hz), 7.57-7.37 (m, 5H), 7.27-7.14 (m, 5H), 7.01 (d, 1H, *J* = 14.3 Hz), 6.29 (dd, 1H, *J* = 10.0, 14.3 Hz), 4.02 (dt, 1H, *J* = 3.0, 10.7 Hz), 3.70 (dd, 1H, *J* = 3.0, 13.7 Hz), 3.03 (dd, 1H, J = 11.5, 13.5 Hz); ^{13}C NMR δ_C 146.1, 136.9, 135.9, 134.2, 131.1, 129.2, 129.1, 128.8, 128.6, 127.1, 124.8,

120.4, 111.9, 109.7, 68.7, 34.2. Anal. Calcd for $C_{22}H_{19}N_3O_2S$: C, 67.85; H, 4.92; N, 10.79. Found: C, 67.59; H, 4.96; N, 10.82.

(*E*)-1-(Benzotriazol-1-yl)- 3-phenylsulfonyl-1-butene (**5.10b**). The title compound was made by the reaction of compound **5.6a** with methyl iodide by Method A. It could not be separated from compound **5.11b** by chromatography.

(*E*)-1-(Benzotriazol-1-yl)-3-phenylsulfonyl-1-heptene (**5.10c**). The title compound was obtained by the reaction of compound **5.6a** with *n*-butyl bromide by Method A in 18% yield as a yellow oil; ^{1}H NMR δ_H 8.10 (d, 1H, *J* = 8.3 Hz), 7.90 (d, 2H, *J* = 7.6 Hz), 7.67-7.42 (m, 6H), 7.28 (d, 1H, *J* = 14.3 Hz), 6.24 (dd, 1H, *J* = 9.9, 14.3 Hz), 3.76 (dt, 1H, *J* = 2.9, 10.5 Hz), 2.26-2.22 (m, 1H), 1.83-1.72 (m, 1H), 1.47-1.30 (m, 4H), 0.86-0.91 (m, 3H); ^{13}C NMR δ_C 146.3, 137.1, 134.0, 131.2, 129.2, 129.1, 128.9, 128.7, 124.9, 120.5, 112.7, 109.9, 67.5, 28.9, 27.4, 22.2, 13.7. HRMS (FAB) Calcd for $C_{19}H_{21}N_3O_2S$ + H, 356.1433; found 356.1448.

(*E*)-1-(Benzotriazol-1-yl)-4-phenyl-3-(phenylmethyl)-3-phenylsulfonyl-1-butene (**5.11a**). The title compound was obtained from the reaction of compound **5.6a** with benzyl bromide by Method A (6% yield) or Method B (82% yield) as a white solid (acetone), mp 113-116 °C; ^{1}H NMR δ_H 7.97 (d, 1H, *J* = 7.9 Hz), 7.72 (d, 2H, *J* = 7.5 Hz), 7.54 (t, 1H, J = 7.7 Hz), 7.45-7.25 (m, 6H), 7.18-7.02 (m, 10H), 6.43 (d, 1H, *J* = 14.8 Hz), 3.40 (s, 4H); ^{13}C NMR δ_C 146.2, 135.8, 134.8, 133.9, 131.1, 130.9, 129.1, 128.7, 128.5, 128.2, 127.2, 124.8, 120.3, 116.0, 109.9, 70.6, 38.2. HRMS (FAB) Calcd for $C_{29}H_{25}N_3O_2S$ + H, 480.1746; found 480.1762.

(*E*)-1-(Benzotriazol-1-yl)-3-methyl-3-phenylsulfonyl-1-butene (**5.11b**). The title compound was crystallized from the crude reaction mixture of the reaction of compound

5.6a with methyl iodide by Method A (34% yield) or from **5.6a,b** by Method B (total 84% yield for **5.11b** and **5.13b**); the benzotriazol-1-yl isomer was white needles (acetone), mp 167-170 °C; ^{1}H NMR δ_H 8.10 (d, 1H, J = 8.4 Hz), 7.88 (d, 2H, J = 7.4 Hz), 7.71-7.43 (m, 6H), 7.33 (d, 1H, J = 14.6 Hz), 6.64 (d, 1H, J = 14.6 Hz), 1.66 (s, 6H); ^{13}C NMR δ_C 146.3, 134.8, 134.0, 131.2, 130.5, 128.7, 128.6, 126.7, 124.9, 120.4, 119.1, 110.0, 63.6, 21.3. Anal. Calcd for $C_{17}H_{17}N_3O_2S$: C, 62.37; H, 5.23; N, 12.83. Found: C, 62.55; H, 5.20; N, 12.89.

(*E*)-1-(Benzotriazol-1-yl)-3-butyl-3-phenylsulfonyl-1-heptene (**5.11c**). The title compound was obtained from the reaction of compound **5.6a** with *n*-butyl bromide by Method A in 26% yield as a white solid (ethyl acetate), mp 117-118 °C; ^{1}H NMR δ_H 8.10 (d, 1H, J = 8.2 Hz), 7.82 (d, 2H, J = 8.0 Hz), 7.69-7.56 (m, 3H), 7.49-7.43 (m, 3H), 7.21 (d, 1H, J = 14.8 Hz), 6.40 (d, 1H, J = 14.8 Hz), 2.21-2.13 (m, 2H), 1.89 (dt, 2H, J = 13.5, 2.7 Hz), 1.67-1.60 (m, 2H), 1.41-1.40 (m, 6H), 0.96 (t, 6H, J = 6.8 Hz); ^{13}C NMR δ_C 146.4, 135.7, 133.9, 131.2, 130.4, 128.7, 128.6, 127.3, 124.9, 120.6, 119.7, 110.0, 69.8, 30.1, 25.7, 23.3, 13.9. Anal. Calcd for $C_{23}H_{29}N_3O_2S$: C, 67.12; H, 7.10; N, 10.21. Found: C, 67.15; H, 7.34; N, 10.23.

(*E*)-1-(Phenylsulfonyl)-1-[2-benzotriazol-1-yl)vinyl]cyclopentane (**5.11d**). The title compound was obtained by the reaction of compound **5.6a** with 1,4-dibromobutane by Method B (only 1 equiv of electrophile) in 64% yield; white needles (ethyl acetate), mp 176-177 °C; ^{1}H NMR δ_H 8.12 (d, 1H, J = 8.2 Hz), 7.86 (d, 2H, J = 7.7 Hz), 7.68-7.57 (m, 3H), 7.51-7.43 (m, 3H), 7.30 (d, 1H, J = 14.8 Hz), 6.53 (d, 1H, J = 14.6 Hz), 2.65-2.59 (m, 2H), 2.02-2.00 (m, 4H), 1.81-1.77 (m, 2H); ^{13}C NMR δ_C 146.4, 136.5, 133.8, 131.2,

130.1, 128.8, 128.7, 127.2, 124.9, 120.5, 119.0, 110.0, 73.6, 33.3, 24.4. Anal. Calcd for $C_{19}H_{19}N_3O_2S$: C, 64.57; H, 5.42; N, 11.89. Found: C, 64.25; H, 5.52; N, 11.81.

(*E*)-1-(Benzotriazol-2-yl)-3-phenylsulfonyl-4-phenyl-1-butene (**5.12**). The title compound was obtained from the reaction of compound **5.6b** with benzyl bromide using Method A as a white solid (ethyl acetate) in 38% yield, mp 189-191 °C; ^{1}H NMR δ_H 7.93 (d, 2H, *J* = 7.7 Hz), 7.81-7.77 (m, 2H), 7.64 (t, 1H, *J* = 7.4 Hz), 7.58-7.50 (m, 2H), 7.39-7.35 (m, 2H), 7.26-7.15 (m, 5H), 6.92 (d, 1H, *J* = 14.0 Hz), 6.74 (dd, 1H, *J* = 10.1, 14.0 Hz), 3.98 (dt, 1H, *J* = 11.3, 2.8 Hz), 3.72 (dd, 1H, *J* = 2.8, 13.7 Hz), 3.04 (dd, 1H, *J* = 11.6, 13.5 Hz); ^{13}C NMR δ_C 144.8, 136.9, 135.9, 134.1, 134.0, 129.2, 129.1, 128.8, 127.7, 127.6, 127.1, 118.2, 116.2, 68.4, 34.1. Anal. Calcd for $C_{22}H_{19}N_3O_2S$: C, 67.85; H, 4.92; N, 10.79. Found: C, 67.52; H, 4.53; N, 10.81.

Chapter 6
SUMMARY AND CONCLUSIONS

Making use of some of the versatile properties of the synthetic auxiliary benzotriazole, the synthesis and utility of several types of benzotriazole-containing intermediates has been explored.

Chapter 2 describes the Reformatsky reaction of bromofluoroacetates with *N*-(*alpha*-aminoalkyl)benzotriazoles, and shows its utility in the synthesis of mono- and di-fluorinated *beta*-amino esters **2.4a-f** and **2.5a-c**, respectively. In addition to supplementing other methods for synthesizing such compounds, this approach has led to the first synthesis of *alpha*-fluorinated bis(*beta*-amino esters) **2.6a-d**.

Chapter 3 describes an improved method for the synthesis of 1,4-, 1,2,4-, 1,3,4- and 4-substituted tetrahydroquinolines which afforded high yields and utilized readily available, crystalline *N*-(*alpha*-aminoalkyl)benzotriazoles and olefins as starting materials. It was shown that the stereochemistry of the olefin was transferred quantitatively to the product using this method. Additionally, an interesting pattern of reactivity of *N*-(*alpha*-aminoalkyl)benzotriazoles **3.17a-c, 3.18b,c** toward olefins in the presence of Lewis acid was uncovered. The presently reported protocol is superior to other previously reported methods in that it (1) utilizes unactivated 1-alkenes and 1,2-disubstituted alkenes and (2) can be employed for the preparation of *N*-unsubstituted and 2-substituted tetrahydroquinolines.

Chapter 4 describes attempts to ascertain the scope and limitations of selected methods of synthesizing *alpha*-benzotriazolylenamines and demonstrate the potential utility of *alpha*-benzotriazolylenamines as stable analogs to *alpha*-chloroenamines. A variety of *alpha*-(benzotriazol-1-yl)enamines **4.20a-g**, **4.21a-f** and **4.22a** were easily prepared as separated E and Z isomers in good overall yields from the action of BtH, $POCl_3$, and NEt_3 on amides **4.16a-g**. Additionally, *N*-[(*E*)-1-(2*H*-1,2,3-benzotriazol-2-yl)-1-butenyl]-*N*-methylaniline (**4.22b**) was synthesized along with *N*-[(*Z*)-1-(1*H*-1,2,3-benzotriazol-1-yl)-1-butenyl]-*N*-methylaniline (**4.20a**) in moderate yield by reaction of *N*-(*trans*-buten-1-yl)-*N*-methylaniline (**4.16**) with 1-chloro-1*H*-1,2,3-benzotriazole (**4.14**) and *t*-BuOK. The utility of these stable compounds was demonstrated by the nucleophilic substitution of the benzotriazolyl moiety from compound **4.22a** by phenylethynylzinc chloride to form *N*-methyl-*N*-[2-methyl-1-(2-phenylethynyl)-1-propenyl]aniline (**4.26**).

In Chapter 5 the synthesis of (*E*)-1-benzotriazolyl-3-(phenylsulfonyl)-1-propene (**5.6**) and its reactivity towards electrophiles was described. A temperature study showed that products formally derived from reaction of alkyl halides with the dianion of (*E*)-1-benzotriazolyl-3-(phenylsulfonyl)-1-propene were formed even when only 1.0 equiv of LDA was utilized. It was also shown that the use of 2.1 equiv of LDA and electrophile gave high yields of *alpha*, *alpha*-dialkylated products. The easy generation of the first carbanion and the carbanion of the monoalkylated compound, and also the regioselectivity in the alkylation of compound **5.6**, was attributed to the greater capability of a sulfonyl group to stabilize an adjacent carbanion as compared to that of a benzotriazolyl group. However, the low reactivity of these carbanions toward electrophiles other than alkyl halides limits the application of this method.

Thus, benzotriazole methodology has been further explored, and thereby resulted in a greater understanding of the benzotriazolyl group, better methods to certain types of compounds and the synthesis of previously unknown entities.

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The reference citation system employed throughout this dissertation is that found in Comprehensive Heterocyclic Chemistry II, Pergamon Press, 1996 (Eds. Katritzky, A. R.; Rees, C. W. and Scriven, E.).

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BIOGRAPHICAL SKETCH

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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